



# Antidepressants, Other

## Therapeutic Class Review (TCR)

August 5, 2014

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## FDA-APPROVED INDICATIONS

Drug	Mfr	Major Depressive Disorder (MDD)	Generalized Anxiety Disorder (GAD)	Social Anxiety Disorder (SAD)	Panic Disorder	Other Indications
bupropion HCl IR (Wellbutrin® IR) <sup>1</sup>	generic	X				
bupropion HCl (Wellbutrin® SR) <sup>2</sup>	generic	X				
bupropion HCl ER (Wellbutrin® XL) <sup>3</sup>	generic	X				prevention of major depressive episodes associated with seasonal affective disorder
bupropion HCl ER (Forfivo XL™) <sup>4</sup>	Edgemont	X				
bupropion HBr (Aplenzin™) <sup>5</sup>	Sanofi	X				
desvenlafaxine fumarate ER (Aptryxol™) <sup>6</sup>	Caraco/Sun Pharma	X				
desvenlafaxine succinate ER (Pristiq®) <sup>7</sup>	Pfizer	X				
desvenlafaxine ER base (Khedezla) <sup>8,9</sup>	generic	X				
duloxetine (Cymbalta®) <sup>10</sup>	generic	X	X			diabetic peripheral neuropathic pain; fibromyalgia; chronic musculoskeletal pain
isocarboxazid (Marplan®) <sup>11</sup>	Validus	X 2 <sup>nd</sup> line therapy				
levomilnacipran (Fetzima) <sup>12</sup>	Forest	X				
mirtazapine tablet & ODT (Remeron®; Remeron SolTab) <sup>13, 14</sup>	generic	X				
nefazodone <sup>15</sup>	generic	X				
phenelzine (Nardil®) <sup>16</sup>	generic	X 2 <sup>nd</sup> line therapy				
selegiline (Emsam®) <sup>17</sup>	Dey	X				

**FDA-Approved Indications (continued)**

Drug	Mfr	Major Depressive Disorder (MDD)	Generalized Anxiety Disorder (GAD)	Social Anxiety Disorder (SAD)	Panic Disorder	Other Indications
tranylcypromine (Parnate®) <sup>18</sup>	generic, GSK	X 2 <sup>nd</sup> line therapy				
trazodone <sup>19</sup>	generic	X				
trazodone ER (Oleptro™) <sup>20</sup>	Labopharm	X				
venlafaxine <sup>21</sup>	generic	X				
venlafaxine ER capsule (Effexor XR®) <sup>22</sup>	generic, Wyeth	X	X	X	X	
venlafaxine ER tablet (Venlafaxine ER) <sup>23</sup>	generic, Upstate	X		X		
vilazodone HCl (Viibryd™) <sup>24</sup>	Forest	X				
vortioxetine (Brintellix) <sup>25</sup>	Takeda Lundbeck	X				

IR = immediate release

SR = sustained release

ER = extended release

**OVERVIEW****Depression**

As many as one-half of all patients with major depressive disorder (MDD) do not experience sufficient symptom improvement despite several adequate trials of antidepressant drugs. Among patients who remit, residual symptoms are common and associated with impaired psychosocial functioning and increased relapse rates. Until recently, known differences among antidepressant drugs were generally limited to safety and tolerability issues. However, over the past few years, a number of studies have emerged to evaluate possible differences among antidepressant classes in their ability to resolve specific symptoms of depression. Each of the groups of drugs in this class has a potential role in the treatment of MDD, primarily as a result of their heterogeneous spectrums of activity. As with many psychotropic drugs, patients failing to respond to one type of antidepressant may respond to a switch to, or augmentation with, an antidepressant with another mechanism of action.

While effectiveness is generally comparable among classes and within classes of antidepressants, the adverse event and safety profiles of the older first generation agents (tricyclic antidepressants, oral monoamine oxidase inhibitors) have greatly reduced their use as first-line agents. The second-generation antidepressants, a heterogeneous group of compounds, are now most commonly used as first- and second-line therapy for MDD. The most commonly prescribed antidepressants, the selective serotonin reuptake inhibitors (SSRIs), are examined in a separate therapeutic class review. These agents, as their name implies, selectively block the reuptake of the neurotransmitter serotonin at the neuronal membrane. It is thought that this enhancement of serotonin activity is primarily responsible for their antidepressant effect.

Other second generation antidepressants exert their effects by inhibiting the reuptake and/or blocking the receptors of one or more of the neurotransmitters thought to be involved in the etiology of depression – dopamine, norepinephrine, and serotonin.

The 2001 algorithm for improved recognition and treatment of depression and anxiety by the International Consensus Group on Depression and Anxiety (ICGDA) recommend SSRIs as first-line therapy for the treatment of depression and anxiety disorders.<sup>26</sup> The majority of the data regarding the use of the non-SSRI second-generation antidepressants for indications other than MDD involves the serotonin/norepinephrine reuptake inhibitors (SNRIs) duloxetine (Cymbalta) and venlafaxine (venlafaxine IR, Effexor XR, Venlafaxine ER).

The 2010 American Psychiatric Association (APA) treatment guidelines for patients with MDD recommend an SSRI, SNRI, mirtazapine, and bupropion as appropriate for initial treatment of most patients.<sup>27</sup> Data showing superiority in efficacy of one or another class of drug (MAOIs, TCAs, SSRIs, SNRIs, and other antidepressants including bupropion, nefazodone, trazodone, or mirtazapine) are not robust or clinically meaningful. They do differ in their adverse event profiles and safety and these characteristics should be considered when choosing an initial therapy. Other factors to consider include drug interaction profiles, pharmacokinetics, patient preference, and historical patient response.

### **Generalized Anxiety Disorder (GAD)<sup>28, 29</sup>**

GAD affects about 6.8 million adult Americans and about twice as many women as men. The disorder develops gradually and can begin across the life cycle, though the risk is highest between childhood and middle age. GAD is diagnosed when a person worries excessively about a variety of everyday problems for at least six months.<sup>30</sup> People with GAD are unable to get rid of their concerns, even though they usually realize that their anxiety is more intense than the situation warrants. Patients cannot relax, startle easily, and have difficulty concentrating. Often, they have trouble falling asleep or staying asleep. Physical symptoms that often accompany the anxiety include fatigue, headaches, muscle tension, muscle aches, difficulty swallowing, trembling, twitching, irritability, sweating, nausea, lightheadedness, having to go to the bathroom frequently, feeling out of breath, and hot flashes. For GAD, the ICGDA recommends SSRIs, SNRIs, tricyclic antidepressants (TCAs), and Cognitive-Behavioral Therapy (CBT) as first-line treatments.<sup>31</sup>

### **Panic Disorder**

Panic disorder is a severe, chronic anxiety disorder characterized by recurrent episodes of panic and the development of fear or anxiety regarding the possibility of future panic attacks. Estimates for the incidence of panic disorder range between three to six million people per year with two-thirds of those affected being female. Epidemiologic studies suggest that up to 15 percent of the general population experience isolated panic attacks, whereas up to 3.5 percent develop full panic disorder during their lifetime.<sup>32</sup> The 2009 American Psychiatric Association (APA) treatment guidelines recommend SSRIs, SNRIs, TCAs, and benzodiazepines as first-line pharmacotherapy for panic disorder. The guideline further states that all are roughly comparable in efficacy, but the relatively favorable safety and side effect profile of SSRIs and SNRIs make them the best initial choice for many patients.<sup>33</sup> SSRIs have the largest evidence base for the condition. Benzodiazepines are appropriate as monotherapy only in the absence of a co-occurring mood disorder and may be useful as adjunct to antidepressants to treat residual anxiety symptoms.

## Social Anxiety Disorder (SAD)<sup>34, 35</sup>

In the United States, SAD is the most common anxiety disorder, affecting approximately 5.3 million people per year. It is the third most common psychiatric disorder after depression and alcohol abuse. This disorder is characterized by a marked and persistent fear of social or performance situations in which embarrassment may occur. Women and men are equally likely to develop the disorder, which usually begins in childhood or early adolescence. There is some evidence that genetic factors are involved. Social anxiety disorder is often accompanied by other anxiety disorders or depression, and substance abuse may develop if people try to self-medicate their anxiety. For SAD, the ICGDA expert panel guidelines recommend SSRIs as first-line therapy.<sup>36</sup>

## Seasonal Affective Disorder<sup>37</sup>

Seasonal affective disorder is characterized by seasonal changes during the year with recurrent episodes of depression usually in the late fall and winter. The depressive episodes alternate with periods of normal or high mood the rest of the year. Seasonal affective disorder is more commonly diagnosed in women, beginning in their twenties, although men also report seasonal affective disorder of similar severity. Many people with seasonal affective disorder report at least one close relative with a psychiatric condition, most frequently a severe depressive disorder (55 percent) or alcohol abuse (34 percent).

Bright white fluorescent light therapy is now considered the first-line treatment intervention and, if properly dosed, it can produce relief within days. Antidepressants may also help and, if necessary, can be used in conjunction with light.

## Traditional and Second-Generation Antidepressants for Other Conditions

The 2008 World Federation of Societies of Biological Psychiatry guidelines recommend SSRIs, SNRIs, and pregabalin as first-line therapies for the treatment of anxiety, obsessive-compulsive, and post-traumatic stress disorders.<sup>38, 39</sup> TCAs are equally effective for some disorders, but many are less well tolerated than the SSRIs and SNRIs. In treatment-resistant cases, benzodiazepines may be used when the patient does not have a history of substance abuse disorders. Although these guidelines focus on medications, non-pharmacological interventions were also considered. CBT and other variants of behavior therapy have been sufficiently investigated in controlled studies in patients with anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder to support them being recommended either alone or in combination with the above medications.

In November 2008, the American College of Physicians released guidelines on the use of second generation antidepressants in the pharmacologic management of acute, continuation, and maintenance phases of MDD, dysthymia, subsyndromal depression, and accompanying symptoms including anxiety, insomnia, and neurovegetative symptoms.<sup>40</sup> The guideline states that existing evidence does not justify the choice of any second-generation antidepressant over another on the basis of greater efficacy. However, four strong recommendations were made regarding antidepressant therapy. The first recommendation is for clinicians to choose pharmacologic therapy for treatment of patients with acute major depression based on adverse effect profiles, cost, and patient preferences. Clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within one to two weeks of initiation of therapy. The American College of Physicians recommends that clinicians modify treatment if the patient does not have an adequate response to pharmacotherapy within six to eight weeks of the initiation of therapy for major

depressive disorder. Lastly, the American College of Physicians recommends that clinicians continue treatment for four to nine months after a satisfactory response in patients with a first episode of MDD. For patients who have had two or more episodes of depression, an even longer duration of therapy may be beneficial.

## PHARMACOLOGY<sup>41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55</sup>

Mechanism of Action	TCAs	SSRIs	MAOIs	NDRIs	Norepinephrine-Serotonin modulators	Serotonin modulators	Serotonin reuptake inhibitor/partial agonist	SNRIs	Clinical and Physiological Effects
			isocarboxazid phenelzine selegiline tranylcypromine	bupropion	mirtazapine	nefazodone trazodone	vilazodone vortioxetine	duloxetine levomilnacipran venlafaxine desvenlafaxine	
Acetylcholine receptor blockade	Yes	No	No	No	No	No	No	No	xerostomia, constipation, sinus tachycardia, memory impairment
Dopamine uptake inhibition	No	No	No	YES	No	No	No	No	antidepressant efficacy, euphoria, anti-Parkinson's activity, aggravation of psychosis
Histamine-1 receptor blockade	Yes	No	No	No	Yes	No	No	No	sedation, antipruritic effect
Monoamine oxidase inhibition	No	No	YES	No	No	No	No	No	antidepressant efficacy, acute hypertension
$\alpha_1$ Norepinephrine receptor blockade	Yes	No	No	No	No	Yes	No	No	orthostatic hypotension, sedation
$\alpha_2$ Norepinephrine receptor blockade	No	No	No	No	YES	No	No	No	antidepressant efficacy, sexual effects
Norepinephrine uptake inhibition	Yes	No	No	YES	No	No	No	YES	antidepressant efficacy, blood pressure, tremors, diaphoresis
Serotonin uptake inhibition	Yes	YES	No	No	No	YES	Yes	YES	antidepressant efficacy, nausea, loose stools, insomnia, anorgasmia
Serotonin receptor blockade	No	No	No	No	Yes	No	No	No	antinausea
Serotonin-2A receptor blockade	Yes	No	No	No	YES	YES	No	No	antidepressant efficacy, REM sleep, anxiolysis, anti-EPS

**Pharmacology (continued)**

Mechanism of Action	TCAs	SSRIs	MAOIs	NDRI	Norepinephrine-Serotonin modulators	Serotonin modulators	Serotonin reuptake inhibitor/partial agonist	SNRIs	Clinical and Physiological Effects
			isocarboxazid phenelzine selegiline tranylcypromine	bupropion	mirtazapine	nefazodone trazodone	vilazodone vortioxetine	Duloxetine levomilnacipran venlafaxine desvenlafaxine	
Serotonin-2C receptor blockade	No	No	No	No	YES	No	No	No	anxiolytic efficacy, appetite, motor restlessness
Serotonin partial agonist	No	No	No	No	No	No	Yes	No	not yet defined

TCA – tricyclic antidepressant, NDRI – norepinephrine dopamine reuptake inhibitor, SNRI – serotonin norepinephrine reuptake inhibitor

The predominant therapeutic effects of each drug are indicated by a capitalized YES.



## PHARMACOKINETICS

Drug	Protein Binding (%)	Half-Life (hr)	Active Metabolites
bupropion HCl (Wellbutrin, Wellbutrin SR, Wellbutrin XL, Forfivo XL) <sup>56, 57, 58, 59</sup>	84	20 - 21	erythrohydrobupropion, hydroxybupropion, threohydrobupropion (half-lives 20-37 hours)
bupropion HBr (Aplenzin) <sup>60</sup>	84	21.3	erythrohydrobupropion, hydroxybupropion, threohydrobupropion
desvenlafaxine fumarate, succinate and base (Apttryxol, Pristiq, desvenlafaxine) <sup>61, 62, 63</sup>	30	11	glucuronide metabolite (19 percent) and N,O-didesmethylvenlafaxine (<5 percent)
duloxetine (Cymbalta) <sup>64</sup>	>90	12	none
isocarboxazid (Marplan) <sup>65</sup>	--	--	--
levomilnacipran (Fetzima) <sup>66</sup>	22	12	None
mirtazapine (Remeron) <sup>67, 68</sup>	85	20 - 40	desmethyl metabolite
nefazodone <sup>69</sup>	>99	11 - 24	hydroxynefazodone, mCPP
phenelzine (Nardil) <sup>70</sup>	--	11.6	none
selegiline (Emsam) <sup>71</sup>	90	18-25	none
tranylcypromine (Parnate) <sup>72</sup>	--	--	--
trazodone <sup>73</sup>	--	5 - 9	m-chlorophenylpiperazine, mCPP
trazodone ER (Oleptro) <sup>74</sup>	89-95	10	m-chlorophenylpiperazine, mCPP
venlafaxine tablet <sup>75</sup>	27	5	O-desmethyl-venlafaxine (half-life 11 hours)
venlafaxine ER capsule (Effexor XR) <sup>76</sup>	27	5	O-desmethyl-venlafaxine (half-life 11 hours)
venlafaxine ER tablet (Venlafaxine ER) <sup>77</sup>	27	10.7	O-desmethyl-venlafaxine (half-life 12.5 hours)
vilazodone HCl (Viibryd) <sup>78</sup>	96-99	25	None
vortioxetine (Brintellix) <sup>79</sup>	98	66	None

bupropion: The peak plasma concentration of bupropion sustained-release (SR) is 85 percent that of immediate-release (IR).<sup>80</sup> Bupropion extended-release (ER) (Wellbutrin XL) has been demonstrated to be equivalent to bupropion IR in terms of bioavailability and peak plasma concentrations. Studies have also shown bioequivalence of bupropion SR and bupropion ER.<sup>81</sup> Bupropion hydrobromide ER (Aplenzin) is an alcohol-resistant formulation. Bupropion ER (Forfivo XL) has demonstrated bioequivalence to bupropion ER (Wellbutrin XL).<sup>82</sup>

desvenlafaxine (O-desmethylvenlafaxine ) is the major active metabolite of venlafaxine. Desvenlafaxine succinate (Pristiq), and the base formulation (desvenlafaxine) provide the same amount of

desvenlafaxine. Desvenlafaxine base and fumarate are bioequivalent but not therapeutically equivalent to desvenlafaxine succinate (Pristiq).

**levomilnacipran (Fetzima):** Levomilnacipran is the more active of the two enantiomers present in milnacipran which is approved for the treatment of MDD outside the US; milnacipran is approved in the US only for the treatment of fibromyalgia. Levomilnacipran is not approved in the US for fibromyalgia. The absorption and bioavailability of levomilnacipran are not significantly affected by food. However, the extended-release formulation of levomilnacipran is affected by alcohol, which may result in a pronounced accelerated drug release, and the two should not be consumed concomitantly.<sup>83</sup>

**nefazodone:** Food decreases the absorption and bioavailability of nefazodone by 20 percent. Liver cirrhosis increases its bioavailability by 25 percent. Nefazodone has a nonlinear pharmacokinetic profile due to autoinhibition via CYP450 3A.<sup>84</sup>

**selegiline:** Selegiline transdermal (Emsam) results in significantly higher exposure to selegiline and lower exposure to its metabolites compared to oral dosing, where extensive first-pass metabolism occurs.<sup>85</sup>

**venlafaxine:** Venlafaxine ER (Effexor XR) has a slower rate of absorption and a lower peak plasma concentration than venlafaxine IR. The extent of absorption of the two dosage forms is equivalent.<sup>86</sup>

**vilazodone (Viibryd):** Food (high fat or light meal) increases the absorption and bioavailability of vilazodone by 72 percent.<sup>87</sup>

**vortioxetine (Brintellix):** The absorption and bioavailability of vortioxetine are not affected by food.<sup>88</sup>

## **CONTRAINDICATIONS/WARNINGS<sup>89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103</sup>**

### **Black box warning**

Antidepressants have a black box warning regarding the risk of suicide. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults compared to placebo in short-term studies of MDD and other psychiatric disorders. Anyone considering the use of any antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.

### **Class warnings**

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed, although not established in controlled trials, that treating such an episode with an antidepressant alone may increase the likelihood of precipitating a mixed/manic episode in patients at risk for bipolar disorder. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history including a family history of suicide, bipolar

disorder, and depression. The antidepressants in this review are not approved for use in treating bipolar depression.

The development of a potentially life-threatening serotonin syndrome may occur with MAOIs, SNRI, SSRI, and other serotonergic drugs like mirtazapine, vilazodone or **vortioxetine**, particularly with concomitant use of other serotonergic drugs, including triptans, and with drugs which impair metabolism of serotonin, including MAOIs. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Concomitant use of these agents with a triptan requires careful observation of the patient, particularly during treatment initiation and dosage increases. Concomitant use of these agents with serotonergic or anti-dopaminergic agents, including antipsychotics, should be discontinued immediately if signs of serotonin syndrome and/or neuroleptic malignant syndrome emerge. These symptoms may include mental status changes, autonomic instability, neuromuscular aberrations, and/or gastrointestinal symptoms. Supportive symptomatic treatment should be initiated immediately.

SSRIs and SNRIs and other antidepressants with serotonergic properties in this class may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of any SSRI or SNRI and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding.

A gradual reduction in the dose of SNRIs rather than abrupt cessation is recommended whenever possible.

Concomitant use of these agents with serotonin precursors (e.g., tryptophan) is not recommended.

Serotonergic drugs may cause hyponatremia resulting from development of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The risk is highest in elderly patients, those requiring diuretic treatment or in those with volume depletion.

Angle-closure glaucoma has been reported in patients with untreated anatomically narrow angles treated with antidepressants.

## **Medication Guide/Risk Evaluation and Mitigation Strategies (REMS)**

The FDA requires that a medication guide be dispensed with all drugs in this class except trazodone and nefazodone. None of the drugs in this class have a current REMS requirement.

### **bupropion (Wellbutrin, Aplenzin, Forfivo XL)**

Bupropion hydrochloride (Wellbutrin, Forfivo XL) and bupropion hydrobromide (Aplenzin) are contraindicated in patients with a seizure disorder, anorexia and/or bulimia, or undergoing abrupt discontinuation of alcohol or sedatives. Bupropion is contraindicated in patients using other bupropion products, regardless of the indication (e.g., depression, smoking cessation, etc.). It is also contraindicated with MAOIs. Discontinuation of an MAOI for at least two weeks is required prior to

initiating use of bupropion. Bupropion inhibits the reuptake of dopamine and norepinephrine and can increase the risk of hypertensive reactions when used with other drugs that also inhibit the reuptake of dopamine or norepinephrine (e.g., MAOIs including linezolid and intravenous methylene blue).

### **Desvenlafaxine fumarate, succinate and base (Aptryxol, Pristiq and desvenlafaxine)**

Desvenlafaxine is contraindicated for use in patients with hypersensitivity to desvenlafaxine, venlafaxine (venlafaxine IR, Effexor XR, Venlafaxine ER), or any excipients in its formulation.

The concomitant use of desvenlafaxine with an MAOI is contraindicated. Do not use with an MAOI within 14 days of stopping an MAOI. Allow seven days after stopping desvenlafaxine before starting an MAOI. Patients taking desvenlafaxine should not be started on linezolid or intravenous methylene blue. These drugs are MAOIs with indications other than psychiatric illness.

Mydriasis has been reported in association with desvenlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored.

Desvenlafaxine should not be used concomitantly with other drugs containing desvenlafaxine or venlafaxine.

### **duloxetine (Cymbalta)**

Duloxetine is contraindicated in patients with uncontrolled narrow-angle glaucoma.

Concomitant use of duloxetine with MAOIs, including linezolid and intravenous methylene blue, is contraindicated. At least 14 days should elapse between discontinuation of the MAOI and initiating duloxetine; at least five days should elapse between the discontinuation of duloxetine and initiating a MAOI. Twenty-four hours should elapse between the last dose of linezolid or intravenous methylene blue and resumption of therapy with duloxetine.

Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine, especially during the first week of therapy or after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension or are potent CYP1A2 inhibitors and in patients taking duloxetine at doses above 60 mg daily. Consider discontinuation of duloxetine in patients with symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

Duloxetine treatment relative to placebo has been associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. In clinical trials, there was no significant difference in the frequency of sustained elevated blood pressure (three consecutive visits). Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.

Duloxetine should not be prescribed for patients with substantial alcohol use or evidence of chronic liver disease. Post-marketing reports indicated that elevated transaminases, bilirubin, and alkaline phosphatase have occurred when duloxetine has been given to such patients. There have been reports of hepatic failure, sometimes fatal, in patients treated with duloxetine.

Duloxetine has been known to affect urethral resistance. If symptoms of urinary hesitation develop with duloxetine, consideration should be given to the possibility that it might be drug-related.

In studies of diabetic peripheral neuropathic pain, duloxetine was associated with a small increase in mean fasting blood glucose as compared to placebo in a study of up to 52 weeks of therapy. The mean fasting blood glucose increased by 12 mg/dL in the duloxetine group and decreased by 11.5 mg/dL in the routine care group. HbA1c changes were +0.5 percent with duloxetine and +0.2 percent with the routine care group.

Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome (SJS) have been reported with duloxetine. Duloxetine should be discontinued at the first appearance of blisters, peeling rash, mucosal erosions, or any other sign of hypersensitivity if no other etiology can be identified.

### **levomilnacipran (Fetzima)**

Levomilnacipran is contraindicated within 14 days of an MAOI or in a patient being treated with linezolid or intravenous methylene blue.

Similar to other SNRIs, levomilnacipran has been reported to cause an increase in blood pressure and heart rate. Blood pressure and heart rate should be monitored prior to and during therapy. Levomilnacipran should be used with caution in patients with pre-existing heart disease (hypertension, tachyarrhythmias or cardiovascular disease). Patients with pre-existing seizure disorders were excluded from clinical trials and it should not be used in these patients. Levomilnacipran may increase urethral resistance; caution is advised in patients prone to obstructive urinary disorders.

Because milnacipran has been reported to increase hepatic transaminases and cause fulminant hepatitis, levomilnacipran should be avoided in patients with a history of substantial alcohol use or chronic liver disease.

### **mirtazapine (Remeron)**

Mirtazapine is contraindicated for use within 14 days of initiating or discontinuing a MAOI.

Agranulosis and severe neutropenia was reported in pre-marketing clinical trials. If patients develop a sore throat, fever, stomatitis, or other signs of infection and has a low white blood cell count, mirtazapine should be discontinued and the patient closely monitored.

### **nefazodone**

Nefazodone has a black box warning for life-threatening liver failure (risk of one case resulting in death or transplant per 250,000 to 300,000 years of nefazodone treatment).

### **MAOIs – isocarboxazid (Marplan), phenelzine (Nardil), tranylcypromine (Parnate)<sup>104,105,106</sup>**

Isocarboxazid should not be used in patients who are hypersensitive to the drug or its ingredients, with a confirmed or suspected cerebrovascular defect, cardiovascular disease, hypertension, pheochromocytoma, history of liver disease or abnormal liver function tests, or severely impaired renal function.

Phenelzine should not be used in patients who are hypersensitive to the drug or its ingredients or patients with pheochromocytoma, congestive heart failure, severe renal impairment or renal disease, a history of liver disease, or abnormal liver function tests.

Tranlycypromine should not be administered to any patient with a confirmed or suspected cerebrovascular defect or to any patient with cardiovascular disease, hypertension, pheochromocytoma, or history of headache. Tranlycypromine should not be used in patients with a history of liver disease or in those patients with abnormal liver function tests.

Patients taking tranlycypromine or phenelzine should not undergo elective surgery requiring general anesthesia or receive cocaine or local anesthesia containing sympathomimetic vasoconstrictors. The possible combined hypotensive effects of MAOIs and spinal anesthesia should be kept in mind. MAOI therapy should be discontinued at least 10 days prior to elective surgery.

Phenelzine and tranlycypromine should not be administered in combination with MAOIs (including procarbazine [Matulane®]) or dibenzazepine derivatives. Dibenzazepine derivatives include the TCAs, carbamazepine, cyclobenzaprine, perphenazine, amoxapine, maprotiline, and mirtazapine. MAOIs should not be administered together or in rapid succession with other MAOIs or with dibenzazepine-related entities. Hypertensive crises or severe convulsive seizures may occur in patients receiving such combinations. In patients being transferred to phenelzine or tranlycypromine from another MAOI or from a dibenzazepine-related entity, allow a medication-free interval of at least seven days (tranlycypromine) to 10 days (phenelzine). MAOIs are contraindicated in patients receiving guanethidine.

MAOIs are contraindicated with bupropion products, buspirone, meperidine, and dextromethorphan. At least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with the contraindicated drugs.

MAOIs should not be administered in combination with any SSRI. There have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma in patients receiving fluoxetine in combination with a MAOI, and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, fluoxetine and other SSRIs should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least five weeks should be allowed after stopping fluoxetine before starting an MAOI.

At least 14 days should elapse between discontinuation of a MAOI and initiation of therapy with duloxetine, desvenlafaxine, trazodone, trazodone ER (Oleptro), venlafaxine IR, venlafaxine ER (Effexor XR and venlafaxine ER), vortioxetine, levomilnacipran or vilazodone. In addition, at least five days should be allowed after stopping duloxetine, or venlafaxine/venlafaxine ER before starting an MAOI. At least seven days should elapse between stopping desvenlafaxine or levomilnacipran and starting a MAOI, at least 14 days should elapse between discontinuation of vilazodone and starting a MAOI and at least 21 days should elapse between discontinuation of vortioxetine and starting a MAOI. Concomitant use in patients taking MAOIs is contraindicated with duloxetine and venlafaxine products due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs.

MAOIs should not be administered in combination with sympathomimetics, including amphetamines, cocaine, methylphenidate, dopamine, epinephrine, norepinephrine or related compounds, and cold, hay fever, or weight-reducing preparations that contain vasoconstrictors.

The most important reaction associated with MAOIs administration is the occurrence of hypertensive crises, which have sometimes been fatal. These crises are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils, and photophobia. Either tachycardia or bradycardia may be present and can be associated with constricting chest pain. Blood pressure should be monitored. Therapy should be discontinued immediately upon the occurrence of palpitation or frequent headaches during therapy.

Hypertensive crises have sometimes occurred during therapy with MAOIs after ingestion of foods with high tyramine content. In general, the patient should avoid protein foods in which aging or protein breakdown is used to increase flavor such as cheese, sour cream, Chianti wine, sherry, beer, liqueurs, pickled herring, anchovies, caviar, liver, canned figs, dried fruits, bananas, raspberries, avocados, overripe fruit, chocolate, soy sauce, sauerkraut, dry sausage, the pods of broad beans, yeast extracts, yogurt, meat extracts, or meat prepared with tenderizers. Excessive amounts of caffeine should be avoided.

### **selegiline (Emsam)**

As a class, MAOIs have been associated with hypertensive crises caused by the ingestion of foods containing high amounts of tyramine. Data for selegiline (Emsam) transdermal 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Patients receiving higher doses should follow the standard dietary modifications for patients taking MAOIs.<sup>107</sup> MAOIs, including selegiline transdermal, are contraindicated in patients with pheochromocytoma.

### **trazodone (generic, Oleptro)**

The QT/QTc interval can be prolonged by use of trazodone. This may lead to torsades de pointes or arrhythmias. Orthostatic hypotension and syncope have also been reported with trazodone use.



**venlafaxine IR and venlafaxine ER (Effexor XR, Venlafaxine ER)**

Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored.

Venlafaxine therapy is associated with sustained hypertension which is defined as supine diastolic blood pressure  $\geq 90$  mm Hg and  $\geq 10$  mm Hg above baseline on three consecutive visits. Venlafaxine IR studies revealed a dose-dependent increase in blood pressure (placebo: two percent; venlafaxine IR doses  $<100$  mg daily: three percent;  $>100$  to  $\leq 200$  mg daily: five percent;  $>200$  to  $\leq 300$  mg daily: seven percent; and doses exceeding 300 mg daily: 13 percent). In pre-marketing studies with venlafaxine ER (Effexor XR) in MDD, 0.7 percent of patients discontinued treated because of elevated blood pressure. Pre-existing hypertension should be controlled before treatment with venlafaxine. Blood pressure should be monitored on a regular basis.

**vilazodone HCl (Viibryd)**

Serotonin syndrome or neuroleptic malignant syndrome can occur with vilazodone; if this occurs, the drug should be discontinued and supportive treatment administered. Vilazodone should not be used in patients being treated with MAOIs including those not being used to treat psychiatric conditions, such as linezolid or methylene blue. Vilazodone should be used with caution in patients with seizure disorders due to its ability to cause seizures. Vilazodone can cause activation of mania or hypomania, and patients should be screened for bipolar disorder. Vilazodone can increase the risk of bleeding and should be used with caution in patients receiving other drugs that affect coagulation. Hyponatremia associated with SIADH can occur. Post-marketing reports of bruxism have been reported.

**vortioxetine (Brintellix)**

Vortioxetine is contraindicated within 21 days of an MAOI or in a patient being treated with linezolid or intravenous methylene blue.

The warnings and precautions for use of vortioxetine are consistent with the class warnings observed with other serotonergic drugs (described above).



## DRUG INTERACTIONS

The non-MAOI drugs in this class should not be used concomitantly within two weeks of stopping an MAOI. Additionally, when converting from an MAOI to one of these antidepressants, there must be a washout period of seven to 21 days depending on the specific drug. This interaction warning also applies to other non-psychiatric medications with MAOI properties, such as linezolid and intravenous methylene blue.

A more extensive discussion is located in the Contraindications/Warnings section.

The development of a potentially life-threatening serotonin syndrome may occur with SNRIs, SSRIs or other serotonergic antidepressant treatment, particularly with concomitant use of serotonergic drugs in other classes, including triptans.

Serotonergic drugs may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk.

Inhibition potential at CYP450 enzyme systems at usual doses<sup>108,109,110</sup>

Drug	1A2	2C9/19	2B6	2D6	3A4
bupropion HCl (Wellbutrin IR / SR / XL/ Forfivo XL) <sup>111,112</sup>	--	low	low	low	low
bupropion HBr (Aplenzin) <sup>113</sup>	--	--	low	low	--
desvenlafaxine succinate (Pristiq) <sup>114</sup>	--	--	--	low	low
desvenlafaxine <sup>115</sup>					
duloxetine (Cymbalta) <sup>116</sup>	--	--	--	moderate	--
isocarboxazid (Marplan) <sup>117</sup>	--	--	--	--	--
levomilnacipran (Fetzima) <sup>118</sup>	--	--	--	--	--
mirtazapine <sup>119</sup>	low	low	--	low	low
nefazodone <sup>120</sup>	low	low	--	low	high
phenelzine (Nardil) <sup>121</sup>	--	--	--	--	--
selegiline (Emsam) <sup>122</sup>	--	--	--	--	--
tranylcypromine (Parnate) <sup>123</sup>	--	--	--	--	--
trazodone ER (Oleptro) <sup>124</sup>	--	--	--	--	low
venlafaxine (venlafaxine IR, Effexor XR, Venlafaxine ER) <sup>125, 126, 127</sup>	--	--	--	low	--
vilazodone HCl (Viibryd) <sup>128</sup>	--	--	--	--	--
vortioxetine (Brintellix) <sup>129</sup>	--	--	--	--	--

-- = no or negligible inhibition

Low = 20-50% inhibition

Moderate = 50-100% inhibition

High = 100-150% inhibition

## **bupropion (Aplenzin / Wellbutrin SR / Wellbutrin XL, Forfivo XL)**

- drugs metabolized by CYP2D6 – use concurrently with caution; use lower dose of concomitant medication
- levodopa, amantadine – higher incidence of adverse effects
- drugs that lower seizure threshold – increases the incidence of bupropion-related seizures
- other dopamine agonists and norepinephrine antagonists – potentiation and reduction in the effects of these drugs may occur when administered with bupropion
- ritonavir, ritonavir plus lopinavir, and efavirenz reduced the exposure of bupropion and its major metabolites in a dose dependent manner. This is possibly due to the induction of bupropion metabolism.

## **desvenlafaxine succinate (Pristiq) and desvenlafaxine**

- drugs metabolized by CYP2D6 – concomitant use of drugs metabolized by CYP2D6 may result in higher concentrations of that drug
- drugs metabolized by CYP3A4 – concomitant use of drugs metabolized by CYP3A4 may result in lower concentrations of that drug and alternatively higher concentrations of desvenlafaxine

## **duloxetine (Cymbalta)**

- inhibitors of CYP2D6 – concomitant use increases duloxetine concentration
- inhibitors of CYP1A2 – concomitant use increases duloxetine concentration
- drugs metabolized by CYP2D6 – duloxetine is a moderate inhibitor of CYP2D6 and increases the AUC and Cmax of drugs metabolized by this enzyme – use with caution
- drugs that raise the gastric pH – duloxetine is enteric-coated and drugs that raise gastric pH may lead to early release of duloxetine
- drugs that are highly protein-bound – duloxetine is highly protein-bound and administration with another highly protein-bound drug may increase free concentrations of the other drug

## **isocarboxazid (Marplan)**

- disulfiram (Antabuse®) coadministration – cautious administration and monitoring suggested
- combination therapy with other psychotropics – generally not recommended and 10-day wash-out interval suggested to avoid concomitant use

## **levomilnacipran (Fetzima)**

- Strong inhibitors of CYP3A4 – levomilnacipran's metabolism may be decreased by strong inhibitors of 3A4 (ketoconazole) resulting in a clinically meaningful increase in levomilnacipran exposure
- Alcohol affects the extended-release properties of levomilnacipran and levomilnacipran should not be taken with alcohol

## **nefazodone**

- drugs that are metabolized by CYP3A4 – nefazodone inhibits the metabolism and increases the bioavailability of drugs metabolized by that enzyme; caution must be used when using nefazodone concurrently with these drugs
- carbamazepine – the bioavailability of nefazodone is reduced by 95 percent when used concurrently with carbamazepine

## **selegiline (Emsam)**

- Contraindications – SSRIs, SNRIs, mirtazapine, TCAs, bupropion, meperidine, tramadol, methadone, propoxyphene, dextromethorphan, St. John's wort, cyclobenzaprine, carbamazepine, oxcarbazepine, sympathomimetic amines, general anesthesia

## **trazodone (generic, Oleptro)**

- CYP3A4 inhibitors – can inhibit the metabolism of trazodone
- CYP3A4 inducers – can induce the metabolism of trazodone
- phenytoin – elevated levels of phenytoin have been reported with concurrent use
- CNS depressants – trazodone may enhance the response to these products

## **venlafaxine (venlafaxine IR, Effexor XR, Venlafaxine ER)**

- haloperidol – the clearance of haloperidol is reduced and bioavailability increased
- ketoconazole – increased concentrations of venlafaxine and O-desmethyl venlafaxine

Due to lack of test specificity, false-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. False-positive test results may result even following discontinuation of bupropion therapy. Similarly, false-positive urine immunoassay screening tests for PCP and amphetamine have been reported with venlafaxine and desvenlafaxine which persist for several days following discontinuation of the drug. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion, venlafaxine, or desvenlafaxine from amphetamines or PCP.

## **vilazodone HCl (Viibryd)**

- CYP3A4 moderate to strong inhibitors – co-administration with strong inhibitors (e.g., ketoconazole) can increase vilazodone plasma concentrations by approximately 50 percent; vilazodone dose reduction is recommended. Moderate inhibitors of CYP3A4 (e.g., erythromycin) may increase vilazodone concentrations; vilazodone dose reduction is recommended if intolerable adverse reactions occur. No dose reduction is indicated when co-administered with mild inhibitors.
- CYP3A4 inducers – the effect of CYP3A4 induction on vilazodone concentrations has not been studied.
- drugs that interfere with hemostasis – platelet release of serotonin plays an important role in hemostasis. Drugs that interfere with serotonin reuptake have been associated with gastrointestinal bleeding, and concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin may potentiate the bleeding risk. SSRIs and SNRIs have been shown to increase

bleeding risk when co-administered with warfarin, and warfarin therapy should be closely monitored if vilazodone is used with warfarin.

- serotonergic drugs – vilazodone has the potential to cause serotonin syndrome if co-administered with other drugs that affect the serotonergic neurotransmitter system.
- drugs that are highly protein-bound – vilazodone is highly protein-bound, and administration with another highly protein-bound drug may increase free concentrations of the other drug.

### **vortioxetine (Brintellix)**

- a dosage reduction of 50 percent should be considered if vortioxetine is administered with a strong CYP2D6 inhibitor such as bupropion, fluoxetine, paroxetine or quinidine
- strong inducers of CYP – consider increasing the dose of vortioxetine when a strong inducer of cytochrome P450 enzymes (e.g., rifampin, carbamazepine, phenytoin) is administered concurrently for longer than 14 days
- coadministration of vortioxetine with other highly protein bound drugs may result in an increase in the other drug's free concentration

## ADVERSE EFFECTS

Drug	Weight Loss	Weight Gain	Dry Mouth	Nausea	Headache	Agitation	Insomnia	Somnolence	Withdrawals due to AE
bupropion HCl IR (Wellbutrin) <sup>130</sup>	23-28 (14-23)	9-14 (23)	28 (10-18)	23 (19)	26 (22)	32 (22)	19-29 (16)	nr	10 (<10)
bupropion HCl SR (Wellbutrin SR) <sup>131</sup>	14-19 (6)	2-3 (4)	17-24 (7)	13-18 (8)	25-26 (23)	3-9 (2)	11-16 (6)	2-3 (2)	0-2.4 (0.3)
bupropion HCl XL (Wellbutrin XL, Forfivo XL) <sup>132, 133**</sup>	23 (11)	11 (21)	26 (15)	13 (8)	34 (26)	2 (<1)	20 (13)	nr	9 (5)
bupropion HBr ER (Aplenzin) <sup>134*</sup>	nr	nr	≥5	≥5	nr	≥5	≥5	nr	nr
desvenlafaxine succinate (Pristiq) <sup>135</sup>	1-2 (1)	nr	11-25 (9)	22-41 (10)	20-29 (23)	reported	9-15 (6)	4-12 (4)	4.1-12 (3-3.8)
desvenlafaxine <sup>136</sup>	1-2 (1)	nr	11-25 (9)	2-41 (10)	0-29 (23)	rtd	9-15 (6)	4-12 (4)	4.1-12 (3-3.8)
duloxetine (Cymbalta) <sup>137</sup>	reported	nr	14 (6)	25 (9)	16 (15)	reported	11 (7)	11 (3))	9-19.5 (4-11.8)
isocarboxazid (Marplan)	nr	nr	6-9 (4)	4-6 (2)	6-15 (13)	nr	4-6 (4)	0-4 (0)	2-12 (5)
levomilnacipran (Fetzima) <sup>138</sup>	nr	nr	nr	17 (6)	nr	nr	nr	nr	9 (3)
mirtazapine (Remeron) <sup>139</sup>	nr	12 (2)	25 (15)	nr	nr	nr	nr	54 (18)	1.5-16 (0-7)

**Adverse Effects (continued)**

Drug	Weight Loss	Weight Gain	Dry Mouth	Nausea	Headache	Agitation	Insomnia	Somnolence	Withdrawals due to AE
nefazodone <sup>140</sup>	nr	nr	25 (13)	22 (12)	36 (33)	nr	11 (9)	25 (14)	16 (nr)
phenelzine (Nardil) <sup>141</sup>	nr	reported	reported	nr	reported	nr	Reported	nr	nr
selegiline (Emsam) <sup>142</sup>	nr	nr	8 (6)	nr	18 (17)	nr	12 (7)	nr	7.1 (3.6)
tranylcypromine (Parnate) <sup>143</sup>	nr	nr	reported	reported	reported	reported	Reported	nr	nr
trazodone <sup>144</sup>	6 (3)	5 (2)	34 (20)	13 (10)	20 (16)	nr	6 (12)	up to 40	nr
trazodone ER (Oleptro) <sup>145</sup>	nr	nr	25 (13)	21 (13)	33 (27)	1-5	Nr	46 (19)	12.5 (nr)
venlafaxine IR <sup>146</sup>	1	reported	22 (11)	37 (11)	25 (24)	2	18 (10)	23 (9)	19
venlafaxine ER (Effexor XR, Venlafaxine ER) <sup>147</sup>	3	> 1	12 (6)	31 (12)	>2	3 (1)	17 (11)	17 (8)	7-18 5-12
vilazodone HCl (Viibryd) <sup>148</sup>	nr	nr	8 (5)	23 (5)	nr	nr	6 (2)	3 (2)	7.1 (3.2)
vortioxetine (Brintellix) <sup>149</sup>	nr	nr	6-8 (6)	21-32 (9)	nr	nr	nr	nr	5-8 (4)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

\*The most common adverse reactions associated with Aplenzin are twice the placebo rate or more.

\*\*Forfivo XL is bioequivalent to Wellbutrin XL.

bupropion (Wellbutrin, Aplenzin, Forfivo XL): There is a dose-related risk of seizures with the use of bupropion. Seizures occur in roughly 0.1 percent of patients receiving bupropion SR up to 300 mg/day and 0.5 percent of patients receiving bupropion IR up to 450 mg/day. The incidence of seizures increases disproportionately at bupropion IR dosages above 450 mg/day.<sup>150</sup> In patients receiving bupropion IR 600 mg/day, the risk of seizures was estimated to be 10 times that of patients receiving the maximum daily recommended dose of 450 mg. According to the manufacturer, the incidence of seizures in patients taking bupropion ER as a single dose of 450 mg is 0.4 percent.

desvenlafaxine (Pristiq and desvenlafaxine): Cautious use in patients with bipolar disorder, cardiovascular/cerebrovascular disease, and lipid metabolism disorders is recommended.

Dose-related elevations in fasting serum total cholesterol, low density lipoprotein cholesterol (LDL-C), and triglycerides were observed in the controlled studies. Measurement of serum lipids should be considered during treatment with desvenlafaxine.

duloxetine (Cymbalta): Duloxetine increases the risk of elevation of serum transaminase levels. In clinical trials, one percent of patients treated with duloxetine had an elevation of alanine aminotransferase (ALT) over three times the upper limit of normal compared to 0.2 percent of patients receiving placebo. Duloxetine is not recommended for use in patients with hepatic insufficiency or who use substantial amounts of alcohol.

isocarboxazid (Marplan): Isolated cases of akathisia, ataxia, black tongue, coma, dysuria, euphoria, hematologic changes, incontinence, neuritis, photosensitivity, sexual disturbances, spider telangiectasias, and urinary retention have been reported. These adverse effects may necessitate discontinuation of therapy. In rare instances, hallucinations have been reported with high doses, but they have disappeared upon dose reduction or discontinuation of therapy.

levomilnacipran (Fetzima): The most common adverse events reported in clinical trials of levomilnacipran (incidence greater than or equal to five percent and at least twice the rate of placebo) were nausea, constipation, hyperhidrosis, heart rate increase, erectile dysfunction, tachycardia, vomiting and palpitations. Erectile dysfunction and urinary retention appear to be dose related.

mirtazapine (Remeron): In pre-marketing trials, two out of 2,796 patients developed agranulocytosis, and a third patient developed severe neutropenia. All three patients recovered upon discontinuation of mirtazapine. These cases yield a crude incidence of severe neutropenia of approximately 1.1 per 1,000 patients (95% CI, 0.2-3.1 cases per 1,000). In clinical trials, nonfasting cholesterol elevations to 20 percent of the upper limit of normal were observed for 15 percent of patients treated with mirtazapine compared to seven percent of patients treated with placebo. Nonfasting triglyceride elevations to 500 mg/dL were observed in six percent of patients treated with mirtazapine, compared to three percent of patient receiving placebo. ALT elevations to three times the upper limit of normal were observed in two percent of patients exposed to mirtazapine compared to 0.3 percent of placebo patients.

nefazodone: There have been reports of adverse liver toxicities with nefazodone. Nefazodone has been removed from the European market based on deaths due to liver failure. Petitions have also been sent to the FDA asking for removal of this product from the US market.

selegiline (Emsam): Application site reactions have been reported in 24 to 36 percent of patients receiving selegiline transdermal patches, compared to 12 to 17 percent of patients receiving placebo patches; rash occurred in four and two percent of patients, respectively.<sup>151, 152, 153</sup>

trazodone (generic, Oleptro): Trazodone is associated with the occurrence of sexual dysfunction, including priapism, ejaculation disorders, erectile dysfunction, and decreased libido.

venlafaxine ER (Effexor XR, Venlafaxine ER): Clinically relevant increases in serum cholesterol were recorded in 5.3 percent of venlafaxine-treated patients and none of the placebo-treated patients for at least three months.

There have been spontaneous reports of adverse events occurring upon discontinuation (particularly when abrupt) of the SNRIs. Adverse events include dysphoria, irritability, agitation, dizziness, sensory disturbances, confusion, headache, lethargy, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms reported. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.

vilazodone HCl (Viibryd): In clinical trials, the most common adverse reactions occurring in greater than five percent of patients and in at least twice the rate as in the placebo group were diarrhea (28 percent), nausea (23 percent), vomiting (five percent), and insomnia (six percent). These adverse reactions are similar in nature to those reported with the SSRIs and SNRIs.

Discontinuation symptoms have been reported when other serotonergic drugs are abruptly stopped so gradual reduction is recommended, whenever possible.

vortioxetine (Brintellix): In short-term (six to eight week) clinical trials the most common adverse reactions with an incidence of greater than or equal to five percent and at least twice the rate of placebo were nausea, constipation and vomiting. Nausea was dose related and typically experienced during treatment initiation (median duration two weeks). Approximately ten percent of patients reported nausea at the end of the six to eight week trial.

Discontinuation symptoms have been reported following abrupt discontinuation of 15 to 20 mg/day dosages.

No significant effect on body weight was reported in clinical trials of vortioxetine.



## SPECIAL POPULATIONS<sup>154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165</sup>

### Pediatrics

Studies of SSRIs were the first to show antidepressant efficacy in children. As a result, SSRIs are used most often in the treatment of children with MDD. The SSRIs are also first-line agents for the treatment of anxiety disorders in children. Non-SSRI antidepressants are most often used as first line therapy in children in the presence of comorbidities, such as attention-deficit/hyperactivity disorder (ADHD), where bupropion (Wellbutrin) may be more effective than an SSRI.<sup>166</sup>

All of the antidepressants in this class have a black box warning regarding suicidality in children, adolescents, and young adults:

A meta-analysis of randomized controlled trials assessed the efficacy and risk of reported suicidal ideation/suicide attempt of antidepressants for treatment of pediatric MDD, obsessive-compulsive disorder (OCD), and non-OCD anxiety disorders.<sup>167</sup> Studies were published and unpublished randomized, placebo-controlled, parallel-group trials of second-generation antidepressants (SSRIs, nefazodone, venlafaxine, and mirtazapine) in participants younger than 19 years of age. Selection included 27 trials of pediatric MDD (n=15), OCD (n=six), and non-OCD anxiety disorders (n=six), and risk differences for response and for suicidal ideation/suicide attempt were estimated by random-effects methods. Pooled risk differences in rates of primary study-defined measures of responder status significantly favored antidepressants for MDD (11 percent; [95% CI, 7.1 to 14.9 percent]), OCD (19.8 percent [95% CI, 13 to 26.6 percent]), and non-OCD anxiety disorders (37.1 percent [95% CI, 22.5 to 51.7 percent]), corresponding to a number needed to treat of 10 (95% CI, seven to 15), six (95% CI, four to eight) and three (95% CI, two to five), respectively. While there was increased risk difference of suicidal ideation/suicide attempt across all trials and indications for drug versus placebo, the pooled risk differences within each indication were not statistically significant. There were no completed suicides. Age-stratified analyses showed that for children younger than 12 years of age with MDD, only fluoxetine showed benefit over placebo. In MDD trials, efficacy was moderated by age, duration of depression, and number of sites in the treatment trial. Relative to placebo, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. Benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.

Safety and effectiveness in the pediatric population have not been established for products in this class. Although no studies have been designed to primarily assess venlafaxine's impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that venlafaxine may adversely affect weight and height.

Transdermal selegiline (Emsam) should not be used at any dose in children under the age of 12, even with dietary modification. Pharmacokinetic data in children < 12 years of age suggests that even the lowest dose of commercially available Emsam may result in higher levels of selegiline than those seen in adolescents or adults. Thus, these children may be at an increased risk of hypertensive crisis.

The TORDIA (Treatment of Resistant Depression in Adolescents) study was a National Institute of Mental Health-sponsored, 12-week, double-blind, randomized, controlled trial of 334 patients aged 12 to 18 years with a primary diagnosis of MDD that had not responded to a two-month initial treatment

with an SSRI.<sup>168</sup> The patients were randomized to one of four groups: (1) switching to a second, different SSRI (paroxetine, citalopram, or fluoxetine, 20-40 mg), (2) switching to venlafaxine ER (150-225 mg), (3) switching to an alternative SSRI and receiving cognitive behavioral therapy (CBT), or (4) switching to venlafaxine ER and receiving CBT. The primary outcome measures were Clinical Global Impressions-Improvement (CGI-I) score of two or less (much or very much improved); a decrease of at least 50 percent in the Children's Depression Rating Scale-Revised (CDRS-R); and change in CDRS-R over time. CBT plus a switch to either medication regimen showed a higher response rate (54.8 percent; 95% CI, 47-62 percent) than a medication switch alone (40.5 percent; 95% CI, 33-48 percent;  $p=0.009$ ), but there was no difference in response rate between venlafaxine ER and a second SSRI (48.2 percent; 95% CI, 41-56 percent versus 47.0 percent; 95% CI, 40-55 percent;  $p=0.83$ ). There were no differential treatment effects on change in the CDRS-R, self-rated depressive symptoms, suicidal ideation, or on the rate of harm-related or any other adverse events. There was a greater increase in diastolic blood pressure and pulse and more frequent occurrence of skin problems during venlafaxine ER than SSRI treatment. For adolescents with depression not responding to an adequate initial treatment with an SSRI, the combination of cognitive behavioral therapy and a switch to another antidepressant resulted in a higher rate of clinical response than did a medication switch alone. However, a switch to another SSRI was just as efficacious as a switch to venlafaxine ER and resulted in fewer adverse effects.

## Pregnancy

For ethical reasons, double-blind, randomized studies of antidepressant drug effects on the fetus and mother are unavailable. Based on animal data, the FDA has classified all of the drugs in this class in Pregnancy Category C. Safety of phenelzine (Nardil) and tranylcypromine (Parnate) for use by pregnant women has not been established.<sup>169, 170</sup> Isocarboxazid (Marplan) should be given to a pregnant woman only if clearly needed.<sup>171</sup>

Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. When treating pregnant women with SNRIs or SSRIs, the physician should carefully consider the potential risks and benefits of treatment. Consider tapering therapy during the third trimester.

## Renal Impairment

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. It should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered. Bupropion ER (Forfivo XL) is only available as a single strength 450 mg dose and is not recommended for use in patients with renal impairment.

Desvenlafaxine (Pristiq) requires a dose adjustment to 50 mg every other day in patients with severe renal impairment or end-stage renal disease (ESRD). Reduce dosage of venlafaxine by 25 to 50 percent in patients with renal impairment and by 50 percent for those on hemodialysis.

Duloxetine (Cymbalta) is not recommended for patients with ESRD or severe renal impairment (estimated creatinine clearance < 30 mL/min).

Isocarboxazid should not be used in patients with severe renal impairment.

In patients with moderate renal impairment (creatinine clearance 30-59 mL/min) the levomilnacipran dose should be not exceed 80 mg/day and for those with severe renal impairment (15-30 mL/min), the maximum daily dose should be 40 mg/day.

Caution is indicated in administering mirtazapine (Remeron) to patients with compromised renal function since its elimination is correlated with creatinine clearance.

## Hepatic Impairment

Bupropion should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced dose and frequency is required. Bupropion should be used with caution in patients with hepatic impairment, including mild to moderate hepatic cirrhosis, and a reduced frequency and/or dose should be considered. All patients with hepatic impairment should be closely monitored for possible adverse effects. Bupropion ER (Forfivo XL) is not recommended for use in patients with hepatic impairment.

Desvenlafaxine does not require a dosage adjustment in starting dosage for patients with hepatic disease.

Duloxetine should not be administered to patients with hepatic insufficiency as it increases the risk of elevation of serum transaminase levels. Duloxetine should also not ordinarily be administered to patients with substantial alcohol use.

Isocarboxazid should not be used in patients with a history of liver disease or in those with abnormal liver function tests.

Hepatic elimination plays a minimal role in the elimination of levomilnacipran; no dose adjustment is recommended in patients with mild-to-severe impairment.

Caution is indicated in administering mirtazapine to patients with compromised hepatic function.

Cases of life-threatening hepatic failure have been reported in patients treated with nefazodone. The physician may consider the value of liver function testing for patients treated with nefazodone, and patients should be advised to be alert for signs and symptoms of liver dysfunction such as jaundice, anorexia, gastrointestinal complaints, and malaise and to report them to their doctor immediately should they occur. Nefazodone should be discontinued if clinical signs or symptoms suggest liver failure. Nefazodone should be withdrawn if evidence of hepatocellular injury, such as increased serum AST or ALT levels greater than three times the upper limit of normal develop, and these patients should be presumed to be at increased risk for liver injury if the drug is reinitiated; therefore, these patients should not be considered for re-treatment.

Dosage adjustment for venlafaxine is necessary in hepatically impaired patients as it is well absorbed and extensively metabolized by the liver.

The dosage of vilazodone (Viibryd) does not need adjustment in patients with mild-to-moderate hepatic dysfunction. Whether the dosage needs to be adjusted in patients with severe hepatic dysfunction is unknown.

The dosage of vortioxetine does not need adjustment in patients with renal dysfunction or mild-to-moderate hepatic dysfunction. It has not been studied in patients with severe hepatic dysfunction and thus is not recommended.

## DOSAGES

Drug	Starting Dose	Maintenance Dose	Maximum Dose	Hepatic Impairment	Renal Impairment	Dosage Forms
bupropion HCl IR (Wellbutrin IR)	100 mg twice daily	100 mg three times daily	150 mg three times daily	↓	↓	Tablets: 75, 100 mg
bupropion HCl SR (Wellbutrin SR)	150 mg every morning	150 mg twice daily	200 mg twice daily	↓	↓	ER tablets: 100, 150, 200 mg
bupropion HCl ER (Wellbutrin XL)	150 mg every morning	300 mg every morning	450 mg every AM	↓	↓	ER tablets: 150, 300 mg
bupropion HCl ER (Forfivo XL)	450 mg once daily	450 mg once daily	450 mg once daily	drug not recommended	drug not recommended	ER Tablet: 450 mg
bupropion HBr ER (Aplenzin)	174 mg every morning (equivalent to 150 mg bupropion HCl)	Periodic assessment for maintenance dose determination	522 mg once daily (equivalent to 450 mg bupropion HCl)	↓	↓	ER tablets: 174, 348, 522 mg
desvenlafaxine fumarate (Aptryxol)	50 mg daily	50 to 400 mg daily	400 mg daily	↓	↓	ER tablets as fumarate: 50, 100 mg
desvenlafaxine succinate (Pristiq)	50 mg daily	50 to 400 mg daily	400 mg daily	↓	↓	ER tablets as succinate: 50, 100 mg
desvenlafaxine base	50 mg daily	50 to 400 mg daily	400 mg daily	↓	↓	ER tablets as free base: 50, 100 mg
duloxetine (Cymbalta)	MDD: 20 to 30 mg twice daily GAD and	60 mg/day in one or two doses	MDD and GAD: 120 mg/day All other diagnoses: 60 mg/day	drug not recommended	↓ drug not recommended with severe impairment	Capsules: 20, 30, 60 mg
isocarboxazid (Marplan)	10 mg twice daily	Periodic assessment with incremental dose increases up to 20 mg/week	60 mg/day in two to four doses	drug not recommended	drug not recommended	Tablets: 10 mg
levomilnacipran (Fetzima)	20 mg daily for 2 days, then 40 mg daily	40 to 120 mg once daily, increase in increments of 40 mg at intervals of ≥ 2 days	120 mg once daily	--	↓	Capsules: 20, 40, 80, 120 mg

**Dosages (continued)**

Drug	Starting Dose	Maintenance Dose	Maximum Dose	Hepatic Impairment	Renal Impairment	Dosage Forms
mirtazapine (Remeron)	15 mg every evening	15 to 45 mg every evening	45 mg every evening	↓	↓	Tablets (oral and rapidly dissolving): 7.5 (oral only), 15, 30, 45 mg
nefazodone	100 mg twice daily	150 to 300 mg twice daily	300 mg twice daily	↓	↓	Tablets: 50, 100, 150, 200, 250 mg
phenelzine (Nardil)	15 mg three times daily	15 – 60 mg per day	90 mg per day in divided doses	nr	nr	Tablets: 15 mg
selegiline (Emsam)	6 mg patch daily	6 mg patch daily	12 mg patch daily	--	--	Patches: 6, 9, 12 mg/24 hours
tranylcypromine (Parnate)	30 mg daily in divided doses	30 mg daily in divided doses	60 mg daily in divided doses	nr	nr	Tablet: 10 mg
trazodone	150 mg/day in divided doses	150 to 400 mg/day in divided doses	400 mg/day in divided doses	↓	↓	Tablets: 50, 100, 150, 300 mg
trazodone ER (Oleptro) <sup>172</sup>	150 mg once daily	150 to 375 mg once daily	375 mg daily	nr	nr	Tablets: 150, 300 mg
venlafaxine IR	75 mg/day in two or three doses	150 mg/day in two or three doses	375 mg/day in three doses	↓	↓	Tablets: 25, 37.5, 50, 75, 100 mg
venlafaxine ER (Effexor XR)	37.5 to 75 mg once daily	75 to 225 mg once daily	225 mg once daily	↓	↓	ER capsules: 37.5, 75, 150 mg
venlafaxine ER (Venlafaxine ER)	37.5 to 75 mg once daily	75 to 225 mg once daily	225 mg once daily	↓	↓	ER tablets: 37.5, 75, 150, 225 mg
vilazodone HCl (Viibryd)	10 mg once daily for 7 days then 20 mg once daily for 7 days	40 mg once daily	40 mg once daily	--	--	Tablets: 10, 20, 40 mg
vortioxetine Brintellix	10 mg once daily	20 mg once daily, 5 mg once daily if intolerance	20 mg once daily	--	--	Tablets: 5, 10, 20 mg

Doses are FDA-approved doses for outpatients. -- = no dosage change required ↓ = consideration should be given to reducing the dose and/or dosage frequency. nr = not reported,

Although desvenlafaxine dosages greater than 50 mg/day were shown to be effective in clinical trials (50 to 400 mg/day), no additional benefit was demonstrated. Adverse events and discontinuations were, however, more frequent with dosages exceeding 50 mg/day.<sup>173</sup>

To minimize the risk of seizures, bupropion dose increases should not exceed 100 mg/day in a three-day period and the maximum daily dosage of 450 mg (522 mg of bupropion HBr) should not be exceeded. Increases above 300 mg/day (348 mg/day of bupropion HBr) should only be used in patients with no clinical effects after several weeks of treatment at 300 mg/day. The time between doses should be at least four hours for 100 mg IR doses, six hours for 150 mg IR doses, and eight hours for SR doses. Cautious dose titration can also minimize agitation, motor restlessness, and insomnia. Bupropion HBr ER should be administered once daily as a single dose. Bupropion ER (Forfivo XL) is available only as an extended-release 450 mg tablet. Therapy should not be initiated with the 450 mg dose, rather titration with other bupropion formulations should be utilized to achieve desired doses.

Trazodone ER (Oleptro) tablets are scored and can be broken without affecting the controlled-release properties.

Venlafaxine has an ascending dose-response curve.<sup>174</sup> At the starting dosage of 75 mg/day, venlafaxine produces approximately the same number of responders as do the SSRIs. The percentage of responders increases with higher doses in a manner consistent with the drug's dual mechanism of inhibiting the uptake of serotonin initially and then norepinephrine at higher doses. Consistent with its pharmacology, higher doses of venlafaxine can also cause a higher incidence of serotonin- and norepinephrine-mediated adverse effects, including the potential to increase blood pressure.

Vilazodone (Viibryd) should be taken with food because administration without food reduces bioavailability and inadequate drug concentrations may result.

Levomilnacipran (Fetzima) should not be taken with alcohol because alcohol affects the extended-release properties of the product and a pronounced accelerated drug release may occur.

## CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Fibromyalgia and diabetic peripheral neuropathic pain are not included in this review. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Studies of less than six weeks duration were excluded since this short timeframe may be insufficient to appropriately evaluate the effects of antidepressant agents. Smaller studies of MDD (fewer than 100 patients) were not included in this evaluation. Due to the high loss of patients in psychotropic studies during follow-up, trials with more than 20 percent loss were still considered for inclusion in this review. Studies focusing specifically on the elderly population or on inpatients were excluded because they are



not applicable to the patient population under consideration. Studies that did not use the standard rating scales described below were also excluded.

## Efficacy Scales

The two most common methods of reporting the efficacy results of antidepressant clinical trials are response rates and remission rates. Response is defined as a 50 percent reduction in severity of the depressive syndrome as measured by a standardized scale or a rating of much or very much improved as assessed by a global assessment method. Remission is a full resolution of the depressive syndrome such that the patient scores in the non-depressed range on such a standardized scale. In clinical trials of antidepressants, the percentage of patients who remit on placebo usually ranges from 20 to 30 percent while the remission rate on active drug is generally 45 to 60 percent. In most studies, response rates are 10 to 15 percent higher than the remission rate.

For MDD, two of the most commonly used standardized rating scales are the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS).

**HAM-D** – This scale is used to assess the severity of MDD in patients already diagnosed with an affective disorder. It is the most widely used and accepted outcome measure for evaluating depression severity. The HAM-D is the standard depression outcome measure used in clinical trials presented to the FDA by pharmaceutical companies for approval of New Drug Applications. The standard HAM-D-21 contains 21 questions. The more commonly used HAM-D-17 excludes four questions relating to diurnal variation, depersonalization and derealization, paranoid symptoms, and obsessional and compulsive symptoms. The remaining 17 questions are related to symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels, and weight loss.<sup>175</sup> The HAM-D-17 provides ratings on current DSM-IV symptoms of depression, with the exceptions of hypersomnia, increased appetite, and concentration/indecision.

**MADRS** – This scale measures the effect of treatment on depression severity and, as such, requires a baseline assessment before treatment with subsequent assessments during the course of treatment. The MADRS measures the severity of a number of symptoms, including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation, and restlessness.<sup>176</sup>

Other standardized scales used in the evaluation of the drugs in this class include:

**HAM-A (Hamilton Anxiety Rating Scale)** – This is the most frequently used and accepted outcome measure for the evaluation of anxiety in clinical trials. The HAM-A consists of 14 items, each defined by a series of symptoms such as anxiety, tension, depressed mood, palpitations, breathing difficulties, sleep disturbances, restlessness, and other physical symptoms.<sup>177</sup> It is included in the National Institute of Mental Health's Early Clinical Drug Evaluation Program Assessment Manual, designed to provide a standard battery of assessments for use in psychotropic drug evaluation.

**CGI-I (Clinical Global Impression – Improvement)** – This three-item scale assesses the patient's improvement or worsening.<sup>178</sup>

**CGI-S (Clinical Global Impression – Severity)** – This three-item scale assesses the clinician's impression of the current state of the patient's illness. The rater is asked to consider his total clinical experience with the given population.<sup>179</sup>

**PGI (Patient Global Impression – Improvement)** – Patients use this scale to rate his or her own improvement.

VAS (Visual Analog Scale) – This is one of the most frequently used measurement scales in health care research, most commonly used for the measurement of pain.<sup>180, 181, 182</sup> This scale measures the intensity or magnitude of sensations and subjective feelings and the relative strength of attitudes and opinions about specific stimuli.

LSAS (Liebowitz Social Anxiety Scale) – This is a questionnaire whose objective is to assess the range of social interaction and performance situations those individuals with social phobia may fear and/or avoid. It is also a popular measurement tool used by researchers to evaluate the efficiency of various social anxiety disorder treatments, including pharmacological trials. A modified social anxiety scale exists for children and adolescents.

SPIN (Social Phobia Inventory) – This self-assessment consists of questions that evaluate fear, avoidance, and physiological discomfort.<sup>183</sup>

BPI (Brief Pain Inventory) – This questionnaire provides information on the intensity of pain (sensory dimension) as well as the degree to which pain interferes with function (reactive dimension). The BPI also asks questions about pain relief, pain quality, and the patient's perception of the cause of pain.

QLDS (Quality of Life in Depression Scale) – This is a 34-item, depression-specific, health-related quality of life instrument that assesses the ability and capacity of individuals to satisfy their daily needs.<sup>184, 185</sup>

Q-LES-Q (Quality of Life Enjoyment and Satisfaction Questionnaire) – This is a self-report measure designed to enable investigators to easily obtain sensitive measures of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning.<sup>186</sup>

SDS (Sheehan Disability Scale) – A self-rated, three-item rating scale used to measure the degree of disease-related disability in the domains of work, family, and social relationships. The limitation of this disability rating scale is that some patients may not accurately recognize their degree of disability until after successful treatment.<sup>187</sup>

PAAS (Panic and Anticipatory Anxiety Scale) – A rating scale for treatment efficacy assessment obtained from a daily diary maintained by the study participant and used to measure the number of panic attacks experienced, the number of episodes of anticipatory anxiety, and the percentage of time in each 24-hour period spent worrying about having a panic attack (anticipatory anxiety).<sup>188</sup>

CDRS-R (Children's Depression Rating Scale-Revised) – Modeled after the HAM-D, the CDRS-R is a clinical interview tool designed for assessing six to 12 year-olds, and it has also been used successfully for adolescents. The CDRS-R helps clinicians rate 17 symptom areas: impaired schoolwork, difficulty having fun, social withdrawal, appetite disturbance, sleep disturbance, excessive fatigue, physical complaints, irritability, excessive guilt, low self-esteem, depressed feelings, morbid ideas, suicidal ideas, excessive weeping, depressed facial affect, listless speech, and hypoactivity. It is used to diagnose depression and can be repeated to measure response to treatments.<sup>189</sup>

## Major Depressive Disorder

### *bupropion IR (Wellbutrin IR) and fluoxetine (Prozac®)*

Patients with MDD were, after a one-week placebo phase, randomly assigned to receive bupropion IR 225 to 450 mg/day or fluoxetine 20 to 80 mg/day for six weeks in a double-blind study.<sup>190</sup> The mean daily dose at the end of this 123 patient study was 382 mg for bupropion IR and 38 mg for fluoxetine. There were no statistically significant differences between treatments on any of the efficacy variables.



Response, based on HAM-D, occurred in 63 percent of bupropion treated patients and 58 percent of fluoxetine treated patients ( $p=NS$ ). Response based on CGI scores occurred in 68 and 58 percent of patients, respectively ( $p=NS$ ). HAM-A improved by 59 percent for both treatment groups. There were no significant differences in the improvements in CGI-S and CGI-I. The incidence of treatment-emergent adverse events was low with no statistically significant differences between treatments. The manufacturer of bupropion IR funded the study.

### ***bupropion IR (Wellbutrin IR) and trazodone***

After a one-week placebo lead-in, 124 outpatients with moderate to severe MDD were randomly assigned, in double-blind fashion, to receive bupropion IR 225 to 450 mg/day or trazodone 150 to 400 mg/day for six weeks.<sup>191</sup> Data from the 111 patients used in the efficacy analysis showed that the overall efficacy for each of the two drugs was similar. Improvement in the trazodone treatment group was significantly greater on day seven because of its effect on sleep. At the end of treatment, 58 percent of bupropion-treated patients and 46 percent of trazodone-treated patients were CGI responders. This is equivalent to an odds ratio (OR) for bupropion versus trazodone of  $1.38 / 0.82 = 1.62$  indicating that, based on this study, the odds are 62 percent better for achieving clinical response with bupropion compared with trazodone.<sup>192</sup> Anorexia and anxiety were reported significantly more often for the bupropion group. Somnolence, appetite increase, and edema were reported significantly more often in the trazodone group.

### ***bupropion XL (Wellbutrin XL) and escitalopram (Lexapro®)***

In two identical, double-blind, controlled-trials, 830 patients with MDD were randomized to receive bupropion XL 300 to 450 mg, escitalopram 10 to 20 mg or placebo once daily for up to eight weeks.<sup>193</sup> Pooled data showed a significant difference between escitalopram and placebo, but not bupropion XL and placebo, in HAM-D-17 total scores. There were no significant differences among active treatments with respect to mean change in HAM-D-17, HAM-D-17 response or remission rates, percentage of patients much or very much improved on CGI-I or change in CGI-S.

### ***bupropion (Wellbutrin IR), sertraline (Zoloft®), paroxetine (Paxil®), and escitalopram (Lexapro)***

Six double-blind, randomized clinical trials comparing bupropion ( $n=662$ ) with an SSRI ( $n=655$ ) for the treatment of MDD were pooled to examine whether the treatment of MDD with bupropion results in a greater resolution of sleepiness and fatigue than with the SSRIs: sertraline, paroxetine, or escitalopram.<sup>194</sup> Among the six studies pooled, three studies used sertraline, one used paroxetine and two used escitalopram as the SSRI comparator. Hypersomnia scores were defined as the sum of scores of the Hamilton Depression Rating Scale (HDRS) items #22, 23, and 24. Fatigue scores were defined as the score of HDRS item #13. There was a greater improvement in hypersomnia scores among bupropion-treated than SSRI-treated ( $p<0.0001$ ) or placebo-treated patients ( $p=0.0008$ ). There was also a greater improvement in fatigue scores among bupropion-treated ( $p<0.0001$ ) and SSRI-treated ( $p=0.0005$ ) than placebo-treated patients as well as a greater improvement in fatigue scores among bupropion-treated than SSRI-treated patients ( $p=0.0078$ ). Fewer bupropion-remitters than SSRI-remitters experienced residual hypersomnia (20.5 percent versus 32.1 percent;  $p=0.0014$ ) or residual fatigue (19.5 percent versus 30.2 percent;  $p=0.0020$ ). The manufacturer of bupropion sponsored the study.

***bupropion (Forfivo XL)***

There are no separate, independent clinical trials available to establish the efficacy of the extended-release 450 mg formulation of bupropion.<sup>195</sup> Efficacy in the treatment of major depressive disorder (MDD) was determined from previous trials of the immediate-release formulation of bupropion, as well as data demonstrating bioequivalence of this specific formulation to other extended-release bupropion formulations.

***bupropion (Aplenzin)***

There are no clinical trials available that demonstrate the effectiveness of this bupropion formulation.

***desvenlafaxine base and placebo***

The approval of the base formulation of desvenlafaxine was based on the short-term pivotal clinical trials conducted comparing placebo to the succinate salt; no additional clinical studies were conducted.

***desvenlafaxine succinate (Pristiq) and placebo***

Desvenlafaxine succinate was evaluated in four eight-week, randomized, double-blind, placebo-controlled, fixed-dose studies in adult patients with MDD. Doses studied ranged from 50 mg/day to 400 mg/day. Desvenlafaxine succinate was superior to placebo in improvement in the HAM-D-17 total score (primary endpoint) in all four studies and in the CGI-I in three of the four trials.<sup>196</sup>

Longer-term efficacy was established in two maintenance trials.<sup>197</sup> One study evaluated the longer-term efficacy of desvenlafaxine succinate 50 mg/day using a withdrawal design. Adult patients with MDD and a HAM-D-17 total score  $\geq 20$  (n=548) at baseline who responded to eight weeks of open-label treatment with desvenlafaxine 50 mg/day and had sustained response through week 20 were randomized to placebo or continued desvenlafaxine succinate in a six-month, double-blind, randomized withdrawal period.<sup>198</sup> The primary endpoint, time to relapse (HAM-D-17 total score  $\geq 16$ , discontinuation for unsatisfactory response, hospitalization for depression, suicide attempt, or suicide) was significantly shorter in the placebo group (p<0.001). At six months, the probability of relapse was 30.2 percent in the placebo group compared to 14.3 percent for the desvenlafaxine succinate group. A second similarly designed study evaluated adult patients with MDD who responded to therapy on desvenlafaxine succinate 200 mg/day or 400 mg/day (defined as a HAM-D-17 total score  $\geq 11$  at day 84). Patients were randomized to continue on their same dosage or switch to placebo for up to 26 weeks. At week 26, the probability of relapse was 29 percent in the desvenlafaxine succinate group compared with 49 percent in the placebo group.<sup>199</sup>

A randomized, double-blind, placebo-controlled trial evaluated the short-term efficacy and safety of desvenlafaxine in perimenopausal and postmenopausal women with MDD.<sup>200</sup> Patients (n=387) were randomly assigned to placebo or desvenlafaxine 100 or 200 mg daily for eight weeks. The primary efficacy variable was change from baseline in HAM-D-17 total score, analyzed using a mixed-effects model for repeated-measures analysis. The reduction in adjusted HAM-D-17 total scores from baseline to week eight was significantly greater for desvenlafaxine (-12.64) compared with placebo (-8.33;  $p<0.001$ ). Statistical significance was observed at week one and was sustained through week eight. Response (58.6 percent) and remission (38.2 percent) rates were significantly higher for desvenlafaxine compared with placebo (31.6 percent [ $p<0.001$ ] and 22.4 percent [ $p=0.008$ ], respectively). In total, 7.4 percent of desvenlafaxine patients and 3.2 percent of placebo patients discontinued due to adverse events.

### ***duloxetine (Cymbalta) and escitalopram (Lexapro)***

A randomized, double-blind, placebo- and active comparator-controlled study included patients 18 years of age and older meeting DSM-IV criteria for MDD. Patients received duloxetine 60 mg once daily (n=273), escitalopram 10 mg once daily (n=274), or placebo (n=137).<sup>201</sup> The eight-week study was conducted to compare the speed of onset of antidepressant efficacy for duloxetine and escitalopram and to test whether duloxetine was at least as effective as escitalopram. Onset of efficacy was defined as a 20 percent decrease from baseline on the HAM-D-17 Maier subscale at week two that was maintained or exceeded at all subsequent visits. In this study, both duloxetine and escitalopram showed significantly greater improvement on the primary efficacy measure than placebo over the eight-week acute treatment period, while no differences were observed between drugs or between drugs and placebo on response and remission rates at eight weeks. Escitalopram at a starting dose of 10 mg daily was better tolerated than duloxetine at a starting dose of 60 mg daily as noted by more frequent occurrence of nausea, dry mouth, vomiting, yawning, and irritability for duloxetine-treated patients. This study's pre-defined primary objective was met and showed that duloxetine is not inferior to escitalopram in terms of onset of efficacy.

### ***duloxetine (Cymbalta) and paroxetine (Paxil)***

In a randomized, double-blind trial of eight weeks of active treatment, patients with non-psychotic MDD were randomized to duloxetine 60 mg (n=238) or paroxetine (n=240) once daily.<sup>202</sup> Efficacy was primarily measured on change in the HAM-D-17 using a non-inferiority test with a margin of 2.2. Secondary efficacy measures included the HAM-D-17 subscales, HAM-A, CGI-S, PGI-I, Somatic Symptoms Inventory and VAS for pain. Safety measures included treatment-emergent adverse events, vital signs, weight, laboratory analyses, and electrocardiograms. Non-inferiority of duloxetine to paroxetine was demonstrated because the upper bound of the confidence interval for mean difference in HAM-D-17 change (0.71) was less than the non-inferiority margin. Secondary efficacy endpoints did not differ significantly between treatments with the exception of VAS back pain, where the pooled mean was lower in the duloxetine group (17.1) compared with the paroxetine group (20.3,  $p=0.048$ ). No significant differences were observed in the number of early discontinuations and overall adverse effects; however, a significantly greater proportion of duloxetine-treated patients experienced nausea and palpitations. No clinically relevant changes in other secondary efficacy endpoints were observed with either treatment. This study verifies the utility of duloxetine as an efficacious and safe treatment for both emotional and physical symptoms of MDD in this predominantly Asian patient sample.

***levomilnacipran (Fetzima) and placebo***

Levomilnacipran, 40 to 120 mg once daily, was studied in three 8-week placebo-controlled studies; two were fixed-dose trials and one was a flexible-dose trial. There was no active comparator used in these studies. Adult outpatients with a diagnosis of MDD were enrolled.<sup>203, 204, 205</sup> In all three trials, all doses of levomilnacipran were superior to placebo in improvement of depressive symptoms measured by the MADRS total score at eight weeks. Levomilnacipran was superior to placebo in improvement in the key secondary endpoint, the Sheehan Disability Scale (SDS) for most dosages examined. .

***mirtazapine (Remeron) and paroxetine (Paxil)***

A total of 197 patients with MDD were randomized to 24 weeks of therapy with mirtazapine 30 to 45 mg/day or paroxetine 20 to 30 mg/day in a double-blind manner.<sup>206</sup> Both treatments were efficacious in improving depressive symptomatology, as assessed by group mean HAM-D-17, percentages of HAM-D responders and remitters, and CGI responders. The mirtazapine group showed statistically significantly larger decreases from baseline in the group mean HAM-D-17 at weeks one, two, and four. Statistically significant decreases with paroxetine were seen at weeks two and four. Mirtazapine had a significantly higher incidence of fatigue while paroxetine had significantly more patients complaining of increased sweating, headache, and nausea.

***mirtazapine (Remeron) and sertraline (Zoloft)***

In a double-blind, multicenter study, 345 patients with MDD were randomized to receive mirtazapine orally dissolving tablets 30 to 45 mg/day or sertraline 50 to 150 mg/day for eight weeks.<sup>207</sup> The primary efficacy variable, the mean change from baseline in the HAM-D-17, showed that mirtazapine was significantly ( $p < 0.05$ ) more effective than sertraline at all assessments during the first two weeks of the study. After this time, the HAM-D-17 was similar in both groups. Reduction in sleep disturbance was significantly greater in the mirtazapine group ( $p \leq 0.01$ ). Both drugs also yielded similar effects in terms of HAM-D response, HAM-D remission rate, MADRS, and CGI. Approximately two-thirds of the patients in each treatment group reported at least one adverse event; 13 percent of patients in the mirtazapine group and three percent of the sertraline group withdrew from the study due to adverse events.

***nefazodone and placebo***

A total of 165 outpatients with chronic MDD were enrolled in a randomized trial comparing nefazodone (maximum dose 600 mg/day) and placebo.<sup>208</sup> During the one-year study of maintenance treatment, the occurrence of major depressive episodes was assessed with the HAM-D and a blinded review of symptom exacerbations. At the end of one year, the probability of recurrence was 30.3 percent for nefazodone-treated patients and 47.5 percent for patients receiving placebo ( $p = 0.043$ ). Somnolence was significantly greater among the patients taking active medication (15.4 percent) compared with placebo (4.6 percent).

***phenelzine (Nardil) and tranylcypromine (Parnate)***

Phenelzine and tranylcypromine were compared in a double-blind, flexible dose study with 77 severely depressed patients with treatment resistant depression.<sup>209</sup> Patients had previously been treated with tricyclic antidepressants or fluvoxamine. A total of 87 percent of patients completed the trial with 52 percent of patients responding to therapy. Response was defined as a  $\geq 50$  percent reduction in HAM-D scores. No significant differences in response between both drugs were observed. Seventeen (44 percent) of 39 patients responded to tranylcypromine, and 18 (47 percent) of 38 responded to

phenelzine. The mean reduction in HAM-D score was 10.4 +/- 8.3 for the tranylcypromine sample versus 8.3 +/- 8.4 for the phenelzine-treated patients. Only 10 percent of patients used concomitant psychotropic medication. The most common adverse effects were dizziness, agitation, and insomnia; the incidence was the same in both groups (21 percent).

### ***selegiline (Emsam) and placebo***

Following a one-week placebo lead-in, 177 adults with MDD were randomly assigned to receive selegiline 6 mg/24 hours or placebo transdermally in a double-blind manner for six weeks.<sup>210</sup> At the conclusion of the trial, patients in the selegiline group showed significantly greater improvement than placebo in HAM-D-17 ( $p=0.01$ ), MADRS ( $p=0.005$ ), and CGI-S ( $p=0.007$ ). Most responders showed improvement after one week of treatment. Five percent of patients in each group withdrew from the study due to adverse events. Application site reactions occurred in 36 percent of patients receiving selegiline and 17 percent of those receiving placebo ( $p=0.006$ ).

In a double-blind study, 289 adults with MDD were randomized to receive selegiline 6 mg/24 hour or placebo transdermal patches daily for up to eight weeks.<sup>211</sup> Selegiline was superior to placebo on the MADRS ( $p=0.001$ ), but not on the HAM-D-17 or CGI-S. Side effects were similar in the two groups, with the exception of application site reaction, which occurred in 32 percent of the selegiline-treated patients and 15 percent of placebo-treated patients ( $p=0.001$ ).

In a similar study, 265 patients with MDD were randomized, in double-blind fashion, to receive selegiline 6 mg/24 hour or placebo transdermal patches for eight weeks.<sup>212</sup> Doses could be increased per protocol for patients who failed to show therapeutic response. At the conclusion of the study, selegiline was superior to placebo as measured by the HAM-D-28 and MADRS ( $p\leq 0.05$  for both endpoints).

In a 52-week, double-blind, placebo-substitution, parallel-group clinical trial, safety and efficacy of initial and continuation selegiline in patients with MDD was assessed.<sup>213</sup> After 10 weeks of treatment with selegiline transdermal 6 mg/24 hr, 322 patients who responded with a HAM-D-17 score of ten or less were randomly assigned to double-blind treatment with selegiline transdermal 6 mg/24 hr or placebo for 52 weeks. At study week 52, significantly fewer selegiline patients experienced relapse of MDD episode (25/149 [16.8 percent]) compared with placebo (50/163 [30.7 percent]) ( $p=0.0025$ ). Additionally, patients receiving selegiline transdermal experienced a significantly longer time to relapse compared with those receiving placebo ( $p=0.0048$ ). The safety profile of selegiline transdermal was similar to placebo, with the exception of application-site reactions.

### ***trazodone ER (Oleptro)***

In this double-blind study, 412 patients with MDD were randomized to receive either trazodone ER 150 to 375mg or placebo.<sup>214</sup> Patients continued treatment for six weeks. The primary endpoint was change in the HAM-D-17 total score from baseline to last study visit. There was a statistically significant difference between trazodone ER and placebo on the mean HAMD-17 score (-11.4 versus -9.3,  $p=0.012$ ). A significant difference was present as early as week one and was maintained at all subsequent study visits. The most frequent adverse events were the same for both the treatment and placebo groups: headache and somnolence. There were no clinically significant electrocardiogram or laboratory abnormalities.

***trazodone and fluoxetine (Prozac)***

Outpatients with current nonpsychotic major depressive episodes of at least four weeks duration were given single-blind placebo for one week, after which they were randomized to double-blind treatment with fluoxetine or trazodone for six weeks.<sup>215</sup> The median sustained doses in the 126 patients in the study were 250 mg/day for trazodone and 20 mg/day for fluoxetine. The HAM-D-21 improved similarly in both treatment groups ( $p < 0.001$  for each group compared to baseline). There were no differences between the groups in CGI-S, CGI-I, or PGI-I. More fluoxetine-treated patients reported rhinitis and tremor ( $p \leq 0.05$ ), and more trazodone-treated patients reported somnolence and dizziness ( $p \leq 0.05$ ). More combined events suggesting activation (agitation, anxiety, nervousness, insomnia) were reported with fluoxetine (15.4 percent) than with trazodone (3.3 percent,  $p \leq 0.05$ ). More combined events suggesting sedation (somnolence, asthenia) were reported with trazodone (42.6 percent) than with fluoxetine (21.5 percent,  $p \leq 0.05$ ). Discontinuation rates for activation and sedation did not differ between treatments. The manufacturer of fluoxetine conducted the study.

***venlafaxine IR and fluoxetine (Prozac)***

In an eight-week, multicenter, double-blind, parallel-group study, 382 outpatients with moderate to severe MDD for at least one month were randomized to treatment with venlafaxine IR 37.5 mg twice daily or fluoxetine 20 mg once daily.<sup>216</sup> Daily doses could be doubled after three weeks for poor response. Both drugs produced significant improvements from baseline in mean HAM-D and MADRS ( $p < 0.05$ ), but no significant differences were noted between groups. High response rates were noted with 81 percent in the venlafaxine group and 84 percent in the fluoxetine group achieving that endpoint. Remission was observed in 60 percent of the patients in each group. There were no significant differences in the occurrence of adverse events between groups. The manufacturer of venlafaxine IR funded the study.

In an eight-week double-blind study, 314 patients with MDD were randomized to venlafaxine 37.5 mg twice daily or fluoxetine 20 mg once daily.<sup>217</sup> If the response was inadequate after two weeks of treatment, the dosage of venlafaxine could be increased to 75 mg twice daily. Both treatment groups significantly improved HAM-D, MADRS, and CGI from baseline. While the HAM-D response at week six was higher in the venlafaxine group (72 percent) than the fluoxetine group (60 percent;  $p = 0.023$ ), there was no significant difference at the conclusion of the study. Significantly more patients reported nausea in the venlafaxine group (28 versus 14 percent;  $p = 0.003$ ). The rate of withdrawal from the study due to adverse events was nine percent in the venlafaxine group and four percent in the fluoxetine group.

In a multicenter, double-blind study, 341 patients with MDD and symptoms for more than two weeks were randomized to venlafaxine 75 mg/day or fluoxetine 20 mg/day, each given as fixed doses for 12 weeks.<sup>218</sup> Both treatments significantly improved MADRS, HAM-D-21, and CGI; there were no significant differences between groups. Response was noted in 55 percent of venlafaxine patients and 63 percent of fluoxetine patients. Remission occurred in approximately 35 percent of patients in each group. These low active-treatment remission rates are likely due to the use of a more conservative definition of remission (MADRS  $\leq 6$  rather than the more usual  $\leq 10$ ). There were no significant differences in adverse events between groups.



### ***venlafaxine IR and sertraline (Zoloft)***

In a multicenter, double-blind study, 147 patients with MDD were randomized to receive venlafaxine IR 37.5 mg twice daily or sertraline 50 mg once daily for eight weeks.<sup>219</sup> After two weeks, the doses could be increased to venlafaxine IR 75 mg twice daily or sertraline 50 mg twice daily. There were no significant differences between treatments in mean changes in HAM-D-21, MADRS, or CGI-I, although each improved significantly from baseline. At the conclusion of the study, the HAM-D-21 response rate was higher in the venlafaxine IR group (83 percent) than in the sertraline group (68 percent;  $p=0.05$ ). Similarly, HAM-D-21 remission rates were higher in the venlafaxine IR group than in the sertraline group (68 and 45 percent, respectively;  $p=0.008$ ); this difference was more pronounced in patients who increased the dose. There were no significant differences observed between treatment groups for adverse events. The manufacturer of venlafaxine IR funded the study.

### ***venlafaxine IR and venlafaxine ER (Effexor XR)***

In a double-blind study, 287 patients with MDD were randomized to receive venlafaxine IR 37.5 mg twice daily, venlafaxine ER 75 mg once daily, or placebo for a maximum of 12 weeks.<sup>220</sup> If the response was inadequate after two weeks of treatment, the daily dose of venlafaxine could be increased to 150 mg. Both dosage forms of venlafaxine were significantly superior to placebo beginning at week two for the HAM-D and at week three for the MADRS. Significant improvement in CGI-S began at week six for venlafaxine IR and at week four for venlafaxine ER. Venlafaxine ER exhibited superiority over venlafaxine IR at week 12 for all efficacy variables.

### ***venlafaxine ER (Effexor XR) and escitalopram (Lexapro)***

An eight-week, randomized, double-blind study compared the efficacy and tolerability of escitalopram to venlafaxine ER in 293 primary care patients with MDD.<sup>221</sup> The efficacy of escitalopram 10 to 20 mg was similar to venlafaxine ER 75 to 150 mg, based on mean change from baseline to week eight in MADRS. Response rates were 80 percent in the venlafaxine ER group and 77 percent in the escitalopram group ( $p=NS$ ). Remission rates were 70 percent in each group, although sustained remission was attained nearly one week earlier in the escitalopram group compared to the venlafaxine ER group. More venlafaxine ER-treated patients had nausea, constipation, and increased sweating than patients treated with escitalopram ( $p<0.05$  for each comparison). When treatment was completed after eight weeks, significantly more venlafaxine ER-treated patients had discontinuation symptoms ( $p<0.01$ ).

In a randomized trial, 195 outpatients with MDD received one week of single-blind placebo treatment, followed by eight weeks of double-blind, fixed-dose treatment with either escitalopram or venlafaxine ER, rapidly titrated to 20 mg/day and 225 mg/day, respectively.<sup>222</sup> Mean changes from baseline to endpoint in MADRS for escitalopram and venlafaxine ER were similar. Response rates for the escitalopram and venlafaxine ER groups were 59 and 48 percent, respectively ( $p=NS$ ). Remission rates at endpoint were 41 percent for escitalopram and 37 percent for venlafaxine ER ( $p=NS$ ). The venlafaxine ER group had a higher incidence of treatment-emergent adverse events (85 percent) and discontinuation due to adverse events (16 percent) than the escitalopram group (68 and four percent, respectively;  $p<0.05$  for both comparisons).

***venlafaxine ER (Effexor XR) and fluoxetine (Prozac)***

In a multicenter double-blind study, 301 patients with MDD were randomized to venlafaxine ER 75 to 225 mg/day, fluoxetine 20 to 60 mg/day, or placebo; doses could be increased after two weeks.<sup>223</sup> At the eight-week endpoint, there were no significant differences between the two active treatments on HAM-D-21 or MADRS in the LOCF analysis. Both active treatments significantly improved HAM-D-21 compared to placebo. Only venlafaxine ER improved MADRS and CGI compared to placebo. Venlafaxine ER patients experienced significantly more dizziness and nausea than fluoxetine or placebo patients ( $p < 0.05$ ). The manufacturer of venlafaxine ER funded the study.

***venlafaxine ER (Effexor XR) and sertraline (Zoloft)***

In an eight-week double-blind study, 163 subjects with MDD were randomized to receive venlafaxine ER 75 to 225 mg/day or sertraline 50 to 150 mg/day.<sup>224</sup> There were no significant differences in the effects of the two agents on Q-LES-Q (the primary endpoint), HAM-D, HAM-A, or CGI-S. The lack of difference was also noted for two predetermined subgroups – patients with anxious depression and those with severe depression. Withdrawal due to adverse events occurred in 8.4 percent of venlafaxine ER patients and 3.8 percent of sertraline patients. The manufacturer of sertraline funded this study.

***vilazodone HCl (Viibryd)***

In two eight-week, double-blind studies, patients with MDD were randomized to receive vilazodone 40 mg once daily ( $n=436$ ) or placebo ( $n=433$ ).<sup>225</sup> Patients receiving vilazodone experienced a significantly greater improvement in depressive symptoms compared to placebo-treated patients. In Study 1, the least squares mean difference from placebo in the MADRS score was -3.2 (-5.2, -1.3), and in Study 2, it was -2.5 (-4.4, -0.6),  $p \leq 0.009$  in both studies. Response rates were significantly higher with vilazodone than with placebo on the MADRS ( $p \leq 0.007$ , both studies), HAM-D-17 ( $p \leq 0.026$ , both studies), and CGI-I ( $p \leq 0.004$ , both studies). Treatment emergent adverse events that were reported for vilazodone to a greater extent than with placebo included diarrhea and nausea. Treatment-related effects on sexual function were small and similar to placebo. Effects on weight were not different from placebo.

***vortioxetine (Brintellix) and placebo***

Vortioxetine was evaluated in six short-term six to eight week randomized double-blind, placebo-controlled, fixed-dose studies in patients with MDD.<sup>226</sup> Five were conducted in adults 18 to 75 years of age and the sixth in adults aged 64 to 88 years of age. The dosage of vortioxetine varied among studies from 5 to 20 mg/day with those randomized to 15 or 20 mg/day being titrated up from an initiation dosage of 10 mg/day. In each of the studies, at least one vortioxetine dosage group was superior to placebo in change from baseline in the HAM-D24 or MADRS and each dosage group was superior to placebo in at least one study. Studies conducted in the U.S. showed that the 20 mg/day dosage was the most effective; lower doses were generally not consistently efficacious in U.S. studies but were shown to be effective in studies conducted outside the U.S. Efficacy was typically observed starting at Week 2 with full antidepressant effects observed after Week 4.

A non-U.S. maintenance study was conducted in 639 patients aged 18 to 75 years with MDD (MADRS  $\geq 26$ ) and at least one previous MDD episode. Patients received 12 weeks of open label vortioxetine 5 to 10 mg/day. Patients in remission (MADRS  $\leq 10$ ) at both the ten and 12 Week time point ( $n=396$ ) were then randomized to double-blind treatment with the same dose of vortioxetine ( $n=204$ ) or placebo ( $n=192$ ) for 24 to 64 weeks. Time to relapse (primary endpoint) was significantly longer in the



vortioxetine group compared to the placebo group. Thirteen percent of patients in the vortioxetine group and 26 percent in the placebo group relapsed.<sup>227</sup>

## Generalized Anxiety Disorder (GAD)

### *duloxetine (Cymbalta) and placebo*

Three independent clinical studies were randomized, double-blind, placebo-controlled multicenter studies which were conducted in adult outpatients with DSM-IV-defined GAD. The studies examined the efficacy of duloxetine treatment for improving functional outcomes for patients with GAD.<sup>228</sup> One study compared nine-week, fixed-dose treatment with duloxetine 60 or 120 mg (n=168 and n=170, respectively) with placebo (n=175). The other two studies compared 10-week, flexible-dose treatment with duloxetine 60-120 mg (study two, n=168; study three, n=162) with placebo (study two, n=159; study three, n=161). The main functional outcome measure for each study was the Sheehan Disability Scale (SDS). Duloxetine-treated patients improved significantly more than placebo-treated patients on SDS global functioning (study one,  $p \leq 0.001$ ; studies two and three,  $p \leq 0.01$ ) and SDS work, social life and family/home responsibilities scores ( $p$  values range from  $\leq 0.05$  to  $\leq 0.001$ ). At treatment endpoint, a greater percentage of duloxetine-treated patients had obtained SDS global functioning scores in the normative range than placebo-treated patients ( $p$  values range from  $\leq 0.05$  to  $\leq 0.001$ ). Duloxetine-treated patients also reported greater increases in quality of life, well-being, and health compared with the placebo group on the other functional measures ( $p$  values range from  $\leq 0.05$  to  $\leq 0.001$ ).

In a 10-week, double-blind, flexible-dose trial, 327 adult outpatients with GAD were randomized to duloxetine 60 to 120 mg (n=168) or placebo (n=159) treatment for the evaluation of efficacy, safety, and tolerability of duloxetine in the treatment of GAD.<sup>229</sup> The primary efficacy parameter was mean change from baseline to endpoint HAM-A total score. Patients who received duloxetine demonstrated significantly greater improvement in HAM-A total scores ( $p=0.02$ ); a higher response rate ( $p=0.03$ ), and greater improvement ( $p=0.04$ ) than patients who received placebo. Duloxetine-treated patients were also significantly more improved than placebo-treated patients on SDS global functional ( $p < 0.01$ ) and work, social, and family/home impairment scores ( $p < 0.05$ ). Discontinuation rate for adverse effects was higher for the duloxetine group compared with the placebo group ( $p=0.002$ ). The most common adverse effects with duloxetine were nausea, dizziness, and somnolence.

### *venlafaxine ER (Effexor XR) and placebo*

In a double-blind study, 251 non-depressed outpatients with GAD requiring treatment were randomly assigned to receive either venlafaxine ER or placebo for 28 weeks.<sup>230</sup> The dosage of venlafaxine ER (75, 150 or 225 mg/day) was based on symptom response. During weeks six through 28, response rates in the venlafaxine ER group were at least 69 percent compared with 42 to 46 percent in the placebo group ( $p < 0.001$ ). By an evaluable-patient analysis, venlafaxine ER significantly improved all primary efficacy measures from week one or two through week 28, including the HAM-A, CGI-I, and CGI-S ( $p < 0.001$  for all comparisons to placebo). The most common treatment-emergent adverse event was nausea, followed by somnolence and dry mouth.

In five multicenter, double-blind, clinical trials, 1,839 adult outpatients with GAD were randomized to receive fixed or flexible doses of venlafaxine ER 37.5 to 225 mg/day or placebo.<sup>231</sup> Three trials were eight weeks in duration; two trials were 24 weeks in duration. For the CGI-I, 66 percent of patients aged 60 years or older responded to venlafaxine ER compared to 41 percent of patients on placebo ( $p < 0.01$ ). For patients less than 60 years, comparable figures were 67 percent and 44 percent,

respectively ( $p < 0.001$ ). In older adults, 23 percent of venlafaxine ER patients and 31 percent of placebo patients discontinued treatment prematurely; comparable figures for younger adult patients were 27 percent for the venlafaxine ER group and 28 percent for the placebo group, respectively. Discontinuations due to adverse events were 15 percent and 14 percent for venlafaxine ER and placebo, respectively, in older adults compared with 15 percent and eight percent for younger adults.

In a 24-week, double-blind, parallel-group study, 244 primary care patients with GAD were randomized to receive venlafaxine ER 75 mg or placebo, each given daily.<sup>232</sup> After two weeks, the dose could be doubled if the physician considered the response poor. At 24 weeks, the HAM-A showed improvement in the venlafaxine ER group ( $p = 0.05$  compared to placebo). Remission rates measured at 24 weeks were 28 percent for the venlafaxine ER group and 19 percent for the placebo group ( $p = 0.11$ ).

## Social Anxiety Disorder (SAD)

### *venlafaxine ER (Effexor XR) and placebo*

A multicenter, double-blind trial examined the efficacy and safety of venlafaxine ER in the treatment of generalized SAD.<sup>233</sup> A total of 272 outpatients were randomly assigned to receive either flexible dose venlafaxine ER 75 to 225 mg per day or placebo for 12 weeks. Venlafaxine ER was significantly more effective than placebo as demonstrated by the LSAS at weeks four to 12. Both the CGI-S and CGI-I showed that venlafaxine ER was significantly more effective than placebo at weeks four to 12. Response rates were significantly higher in the venlafaxine ER group throughout the last eight weeks of the study. The FDA-approved dosage of venlafaxine ER for SAD is 75 mg/day.

In a multicenter study, 386 outpatients with SAD were randomized to venlafaxine ER 75 mg/day fixed dose, venlafaxine ER 150 to 225 mg/day flexible dose or placebo.<sup>234</sup> In the double-blind study, improvement on the LSAS, the primary outcome, was greater with either regimen of venlafaxine ER than placebo. This improvement was sustained throughout the six-month trial. Of patients receiving either dose of venlafaxine ER, 58 percent responded to treatment compared to 33 percent of those receiving placebo ( $p < 0.001$ ). Corresponding remission rates were 31 and 16 percent, respectively ( $p < 0.01$ ). There were no differences in outcome between the two venlafaxine ER dosage regimens. The FDA-approved dosage of venlafaxine ER for SAD is 75 mg/day.

### *venlafaxine ER (Effexor XR) and paroxetine (Paxil)*

Four-hundred thirty-four adult outpatients with SAD were randomized to receive venlafaxine ER 75 to 225 mg/day, paroxetine 20 to 50 mg/day, or placebo in a double-blind manner for 12 weeks.<sup>235</sup> Patients with other anxiety or depressive disorders were excluded from the trial. Treatment with venlafaxine ER or paroxetine was associated with significantly greater improvement in LSAS (primary efficacy variable), CGI-I, and SPIN than treatment with placebo ( $p < 0.05$  for all comparisons to placebo). No significant differences in any of the efficacy variables were observed between the venlafaxine ER and paroxetine groups. The week 12 response rates were similar for the venlafaxine ER (69 percent) and paroxetine (66 percent) groups and were significantly higher than the placebo group (36 percent;  $p < 0.05$ ). Both active treatments were generally well tolerated and were associated with a similar incidence of adverse events. The FDA-approved dosage of venlafaxine ER for SAD is 75 mg/day. The manufacturer of venlafaxine ER funded the study.

## Panic Disorder

### ***venlafaxine ER (Effexor XR) and placebo***

In a double-blind trial, 361 adults with panic disorder were randomized to receive venlafaxine ER 75 to 225 mg/day or placebo for up to 10 weeks.<sup>236</sup> In the study, there was no difference between treatment groups in the proportion of patients free from full-symptom panic attacks ( $\geq$  four symptoms), although there were fewer limited-symptom panic attacks in the venlafaxine ER group. Venlafaxine ER was also associated with a lower mean frequency of panic attacks, as well as higher response and remission rates and improvements in anticipatory anxiety, fear, and avoidance.

### ***venlafaxine ER (Effexor XR) or paroxetine (Paxil)***

A total of 664 non-depressed adult outpatients who met DSM-IV criteria for panic disorder (with or without agoraphobia) were randomly assigned to 12 weeks of treatment with placebo or fixed-dose venlafaxine ER 75 mg/day or 150 mg/day, or paroxetine 40 mg/day in a double-blind study in the treatment of panic disorder.<sup>237</sup> The primary measure was the percentage of patients free from full-symptom panic attacks, assessed with the Panic and Anticipatory Anxiety Scale (PAAS). Secondary measures included the Panic Disorder Severity Scale, CGI-S and CGI-I scales; response (CGI-I rating of very much improved or much improved), remission (CGI-S rating of not at all ill or borderline ill and no PAAS full-symptom panic attacks); and measures of depression, anxiety, phobic fear and avoidance, anticipatory anxiety, functioning, and quality of life. Intent to treat, last observation carried forward analysis showed that mean improvement on most measures was greater with venlafaxine ER or paroxetine than with placebo. No significant differences were observed between active treatment groups. Panic-free rates at endpoint with active treatment ranged from 54 to 61 percent, compared with 35 percent for placebo. Approximately 75 percent of patients given active treatment were responders, and nearly 45 percent achieved remission. The placebo response rate was slightly above 55 percent, with remission near 25 percent. Adverse events were similar for active treatment groups and mild to moderate.

## Meta-analyses

The Agency for Healthcare Research and Quality (AHRQ) published its 2011 comparative effectiveness review of second-generation antidepressants in the pharmacologic treatment of adult depression including the diagnoses of MDD, dysthymia and subsyndromal depressive disorders.<sup>238</sup> This report includes studies conducted between 1980 and January 2011. Thirteen drugs are included in the analysis: SSRIs, SSNRIs (duloxetine), SNRIs (desvenlafaxine, mirtazapine, venlafaxine), and other second-generation antidepressants (bupropion, nefazodone, trazodone). Of the 3,722 studies identified, 248 were rated good or fair quality, 228 were included in qualitative synthesis, and 92 in the quantitative synthesis (mixed treatment comparisons and meta-analyses). Key findings for studies of MDD were that, overall, no substantial differences in efficacy or effectiveness were identified among drugs. The authors note that although some comparisons yielded a statistically significant difference, the differences were too small to be considered clinically relevant. Modest differences were identified in onset of action, adverse effects and some measures of health-related quality of life. Notably, data from seven fair quality studies conducted by the manufacturer, show a significantly faster onset of action for mirtazapine compared to four SSRIs, but the pooled number needed to treat (NNT) = 7 to yield one additional responder after one to two weeks. Discontinuation due to adverse effects was higher with duloxetine and venlafaxine when compared to SSRIs. The finding that bupropion has lower

rates of sexual dysfunction compared to several SSRIs is supported by a strength of evidence that is high. It was notable that over the six to 12 weeks of treatment duration, 37 percent of patients did not respond and 53 percent did not achieve remission; there was insufficient data to determine what factors might predict response. Data from 17 studies which included measures of quality of life or functional capacity showed no statistical difference among drugs. Data for dysthymia and subsyndromal depression were insufficient for any comparative conclusion to be made.

One systematic review indicated that, based on fair-to-good evidence, the second-generation antidepressants all have similar efficacy in treating MDD.<sup>239</sup> Of 46 randomized, controlled trials directly comparing agents in this class, all but five reported no statistically significant difference in any outcome measure at the end of the study. Meta-analyses suggest a small, but statistically significant, additional treatment effect for sertraline and venlafaxine compared with fluoxetine.

In another systematic review, researchers analyzed the results of 81 clinical trials involving more than 10,000 adults with MDD that compared newer antidepressants with placebo.<sup>240</sup> Mirtazapine, venlafaxine, nefazodone, and bupropion were among the drugs included in this review, as were several SSRIs. As a group, the newer antidepressants were significantly (60 percent) more effective than placebo. The efficacy of different antidepressant classes was similar, as were the individual agents in each class. A comparison of older antidepressants with newer agents found no significant difference in efficacy with the exception of three studies showing a 20 percent greater effect for an SNRI than for trazodone ( $p=0.05$ ).

A different systematic review of 39 placebo-controlled randomized controlled trials of duloxetine, venlafaxine, and the SSRI, fluoxetine, used meta-regression analysis to compare the relative treatment effect of duloxetine with venlafaxine and fluoxetine in patients with MDD.<sup>241</sup> This analysis found no significant difference in treatment effect, as measured by HAM-D, between duloxetine and fluoxetine. It did, however, identify significantly better efficacy of venlafaxine compared to duloxetine with an OR of 2.0 for the number of responders.

A systematic review of clinical trial data for vilazodone for MDD was published.<sup>242</sup> Investigators identified two eight-week placebo-controlled clinical trials and a one-year open-label safety study. In the pooled data, the NNT calculated for response was eight (95% CI 6-16) and for remission was 14 (95% CI 8-55). The number needed to harm (NNH) for the most common adverse events was six (diarrhea), six (nausea), 30 (vomiting) and 26 (insomnia). Although weight gain was not demonstrated in the eight-week studies, a mean gain of 1.7 kg was reported in the one-year safety study.

## SUMMARY

While all second-generation antidepressants are effective at reducing symptoms of depression, there are no significant differences in efficacy among these agents. This is borne out in data from individual clinical trials, as well as from systematic reviews. Little comparative data is available on vilazodone (Viibryd), vortioxetine (Brintellix) or levomilnacipran (Fetzima). It should be noted that several products have additional indications beyond MDD and anxiety disorders.

These products do, however, have different adverse effect profiles. SSRIs are generally accepted as having mild adverse events. Adverse events reported with vilazodone appear to be similar to those reported with the SSRIs. SNRIs may be as effective as SSRIs, but have more concerning adverse events. Venlafaxine (venlafaxine IR, Effexor XR, venlafaxine ER) is associated with higher rates of nausea and vomiting than fluoxetine. Venlafaxine and desvenlafaxine are also associated with a higher rate of discontinuation syndrome than the second-generation antidepressants. In placebo-controlled trials, discontinuation of duloxetine (Cymbalta) has occurred as a result of higher rates of nausea, vomiting, dizziness, somnolence, and fatigue. Initiation of vortioxetine (Brintellix) is associated with high rates of nausea which appear to dissipate after a median of two weeks on therapy.

For other agents, bupropion (Wellbutrin) appears to have the lowest risk of sexual adverse effects, although reports are variable. Mirtazapine (Remeron) is associated with weight gain most while bupropion results in a net loss of body weight. Mirtazapine, nefazodone, and trazodone (generic, Oleptro) are more likely to cause sedation, but this may be of benefit in patients with depression-related insomnia. Selegiline transdermal (Emsam) is associated with relatively few systemic effects, but it is associated with a high rate of skin reactions.

All of the antidepressants in this class have a black box warning regarding suicidality in children, adolescents, and young adults through the age of 24 years. Related risks as compared to benefits of therapy in this population continue to be evaluated but appear to indicate greater benefit than risk as long as providers, families and caregivers are aware of the risks. Use caution in prescribing these agents and observe patients for signs of these and other adverse effects.

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